

Inflammatory Bowel Disease

趙 H.H. CHAO

COMPREHENSIVE DIGESTIVE DISEASE CENTER

UC IRVINE • HEALTHCARE



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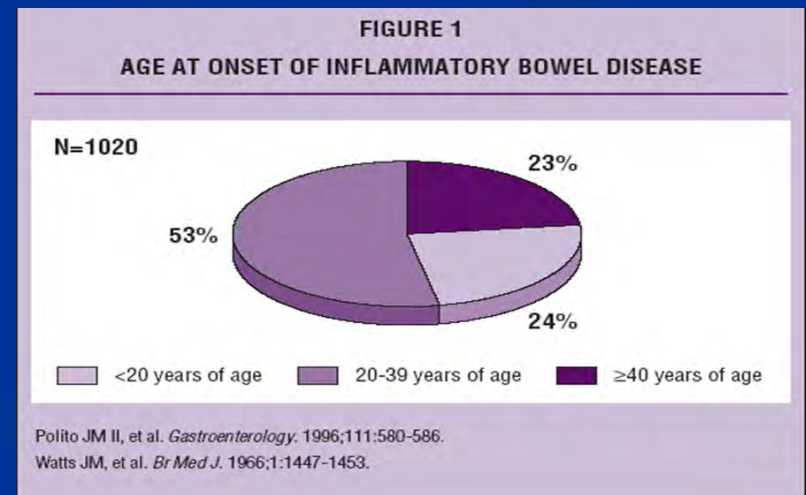
Outline

- Stats and facts of IBD/Epidemiology
- What is Inflammatory Bowel Disease? CD, UC
- Pathogenesis
- Diagnosis
- Therapy
- Surgery



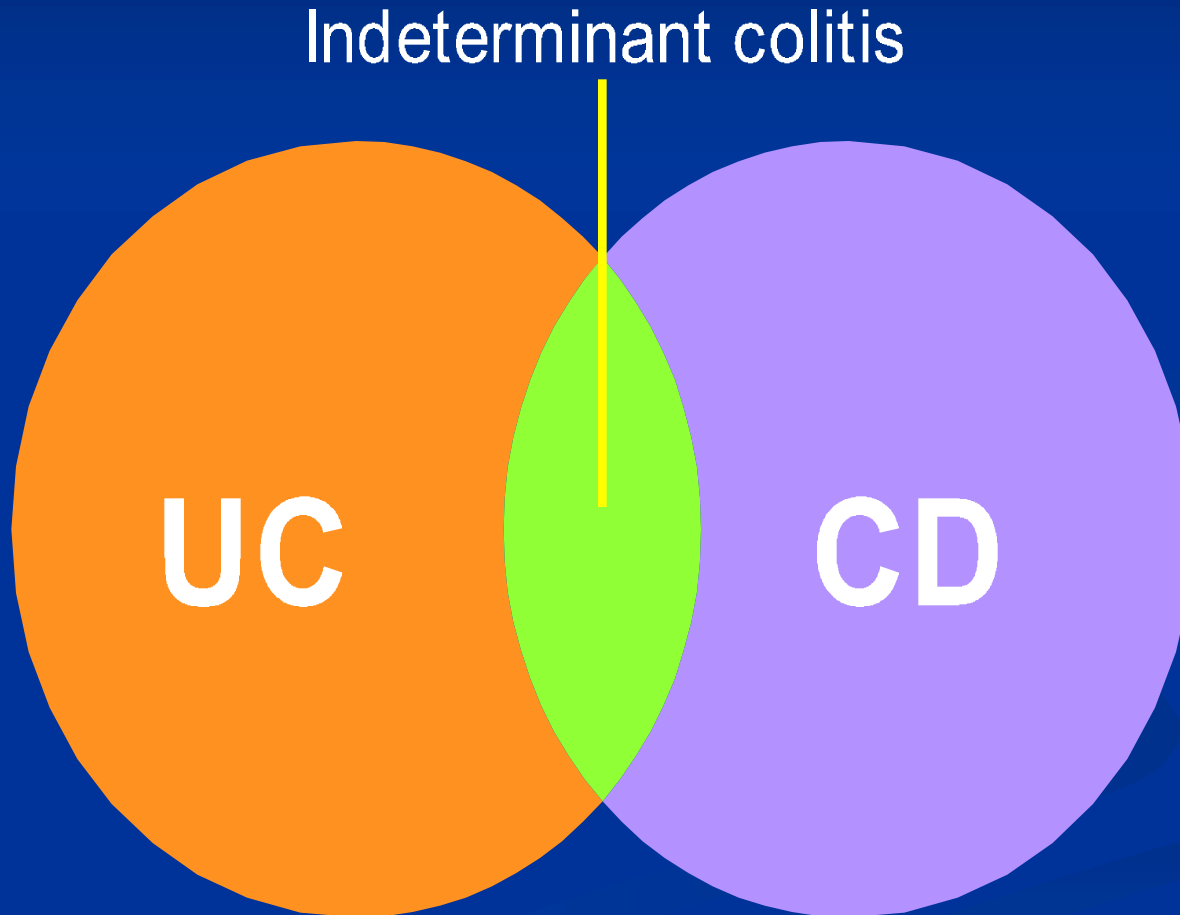
Stats and Facts About IBD

- ❖ There is an estimated 3 million people in the US (1.3% of US pop) suffering from IBD (data as of 2015)
- ❖ Bimodal age of onset is 15 – 30 years old, then 50 – 70 years old
- ❖ Family hx for IBD does affect risk of getting disease
- ❖ If a person has a relative with the disease, his/her risk is estimated to be at least 10 times that of the general population -- 30 times greater if the relative is a sibling.
- ❖ Concordance for
 - site and type of disease
 - Extraintestinal manifestations
 - Age of diagnosis



What is IBD???

The Spectrum of IBD

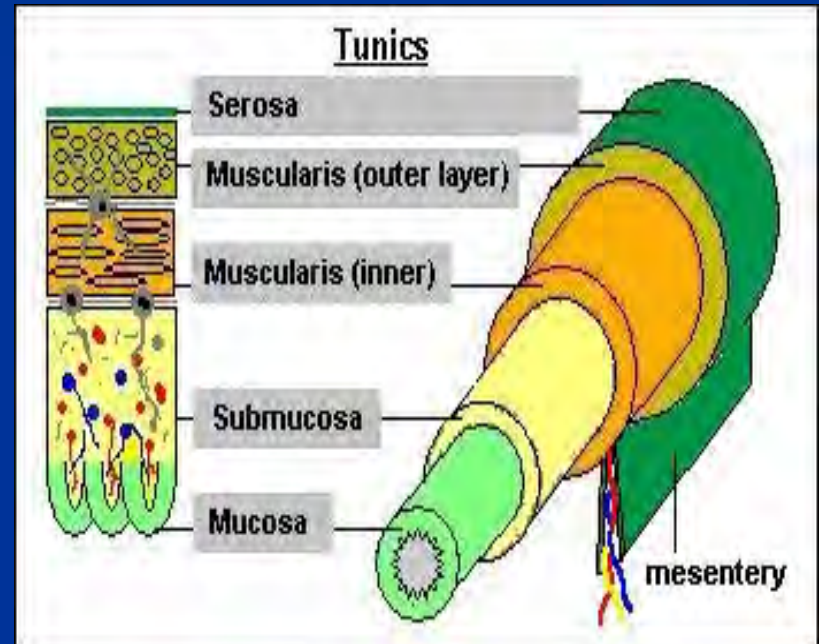


What is IBD?

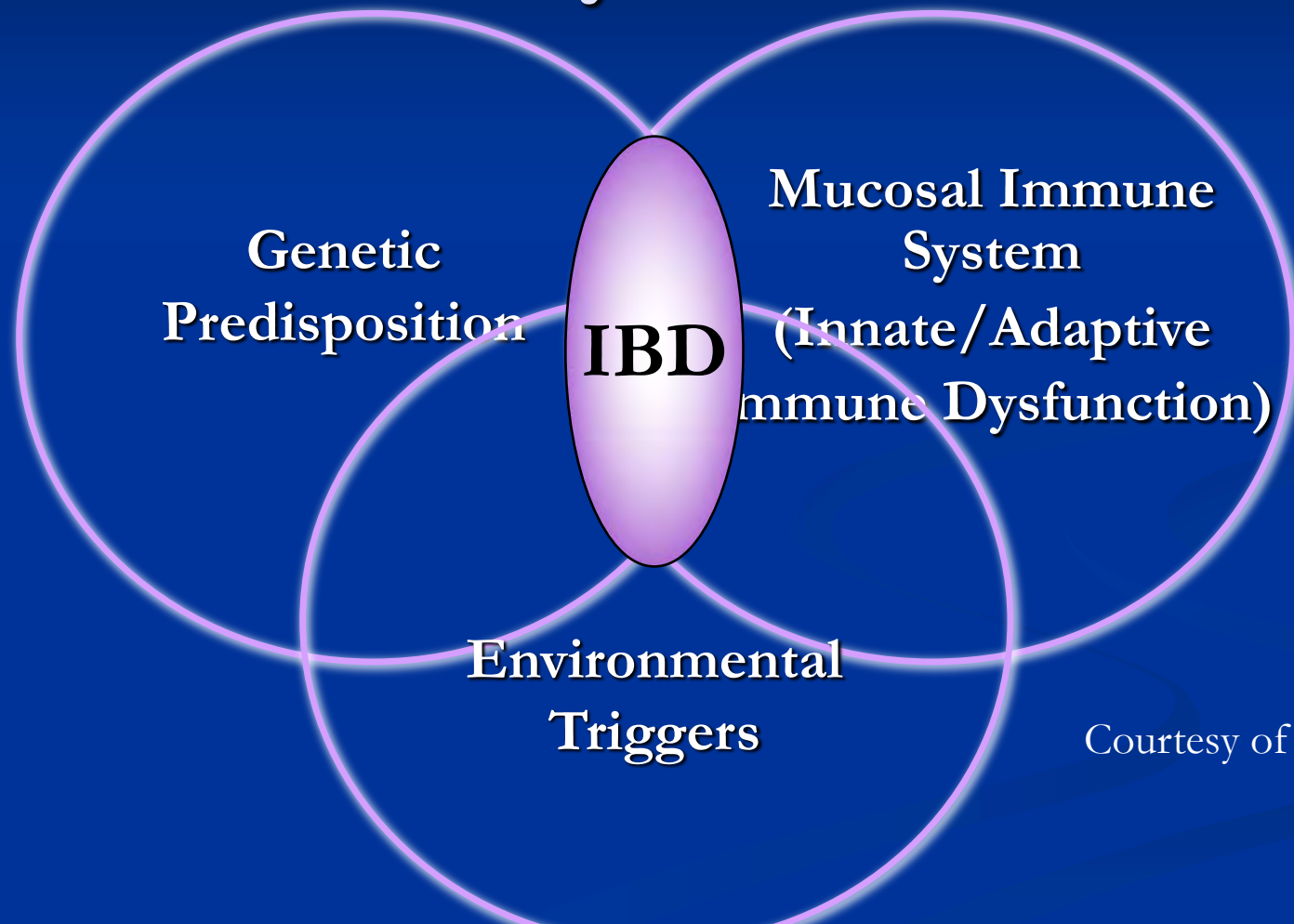
Ulcerative Colitis: A superficial inflammation of the colon only.

- ❖ Mucosa
- ❖ Submucosa

Crohn's Disease: A transmural inflammation from mouth to anus



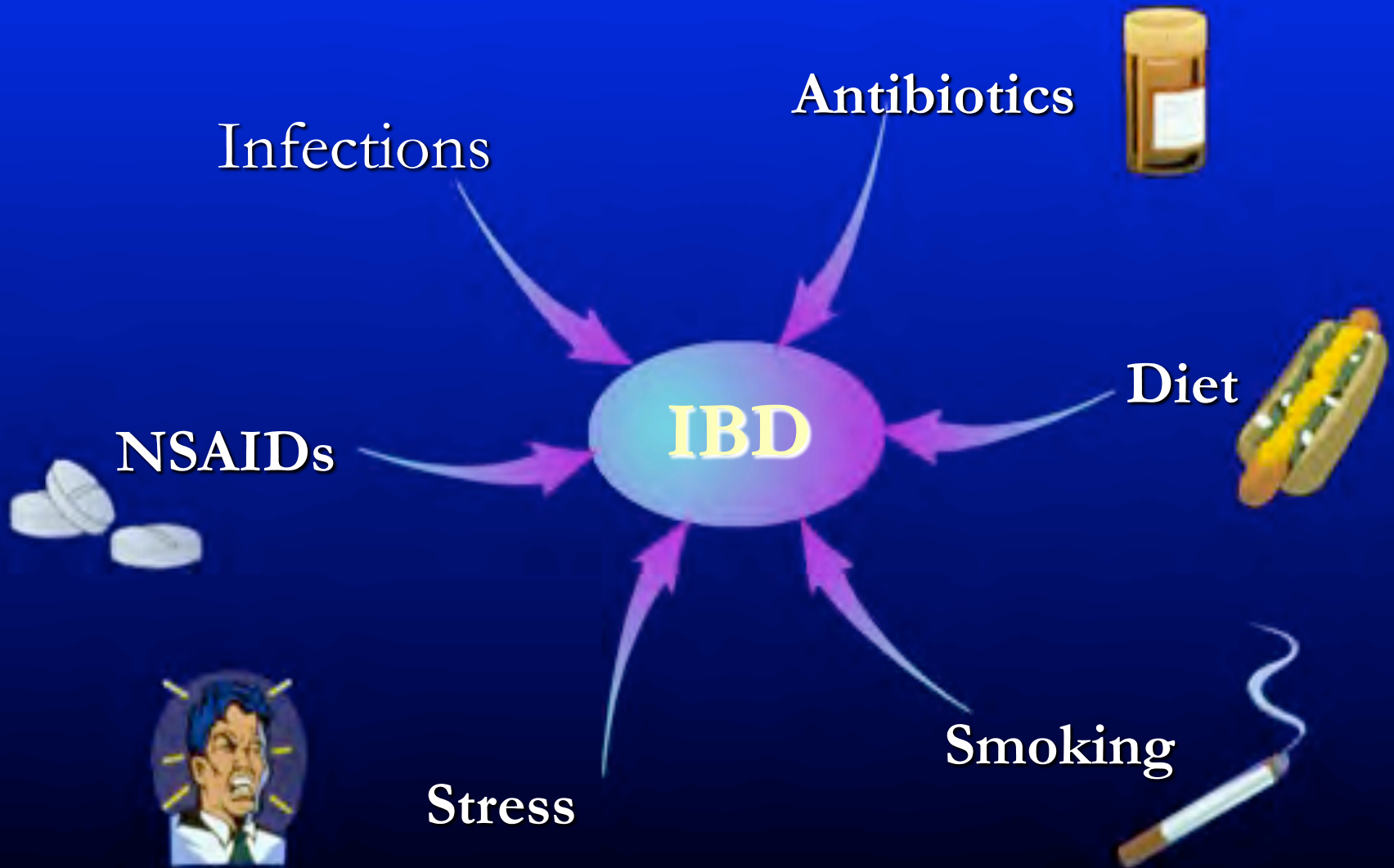
Etiologic Theories in Inflammatory Bowel Disease



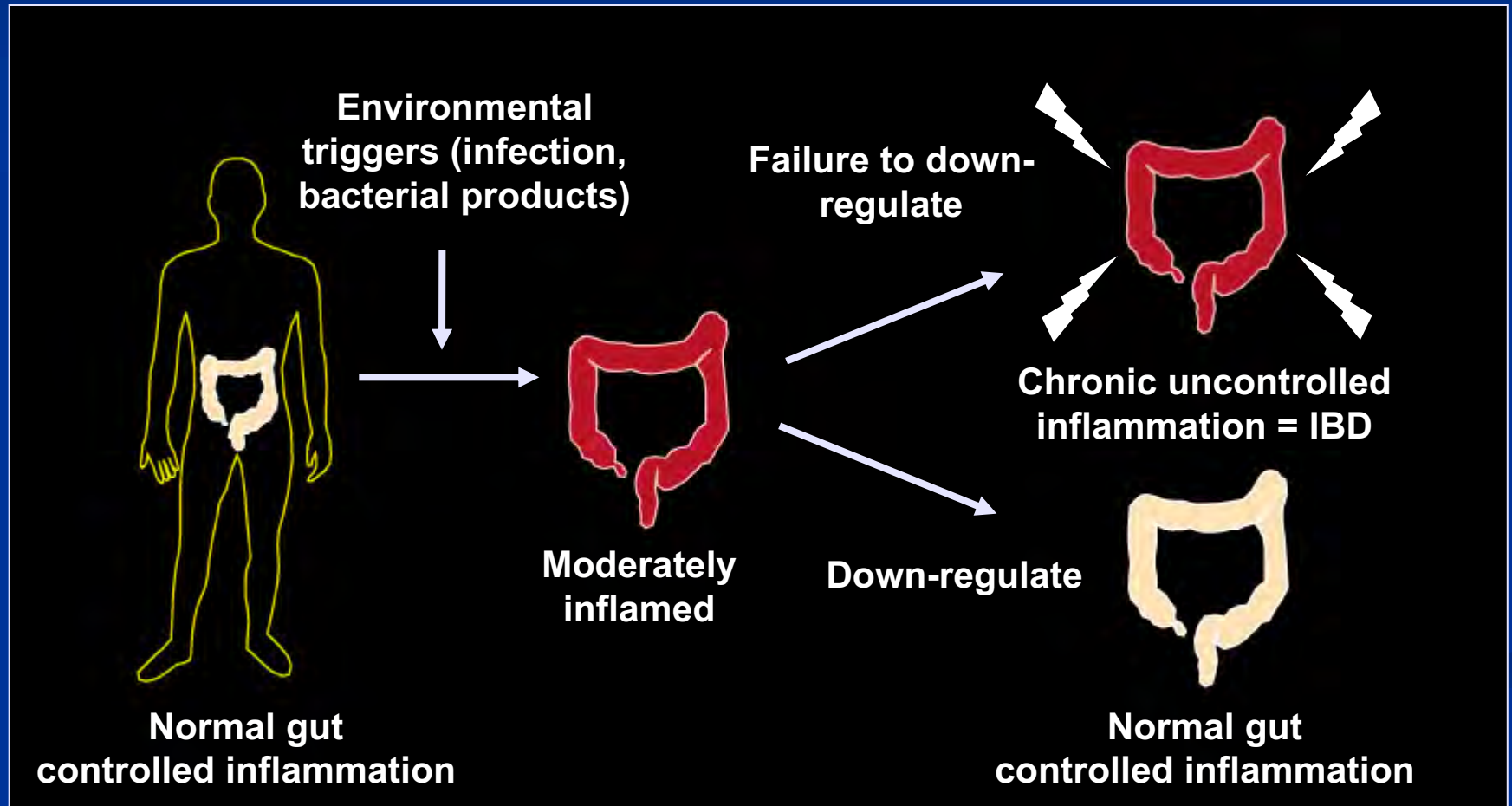
Courtesy of S. Targan



Environmental Triggers



Normal Intestine Vs. Intestine With IBD



Clinical Symptoms

- Diarrhea
- Fecal Urgency
- Hematochezia
- Anal Pain
- Abdominal Pain
- Fevers
- Fatigue
- Weight Loss
- Growth Failure
- Extraintestinal Manifestations
- Stunted growth in children



Symptoms are based on:



Colitis/Diarrhea/Urgency

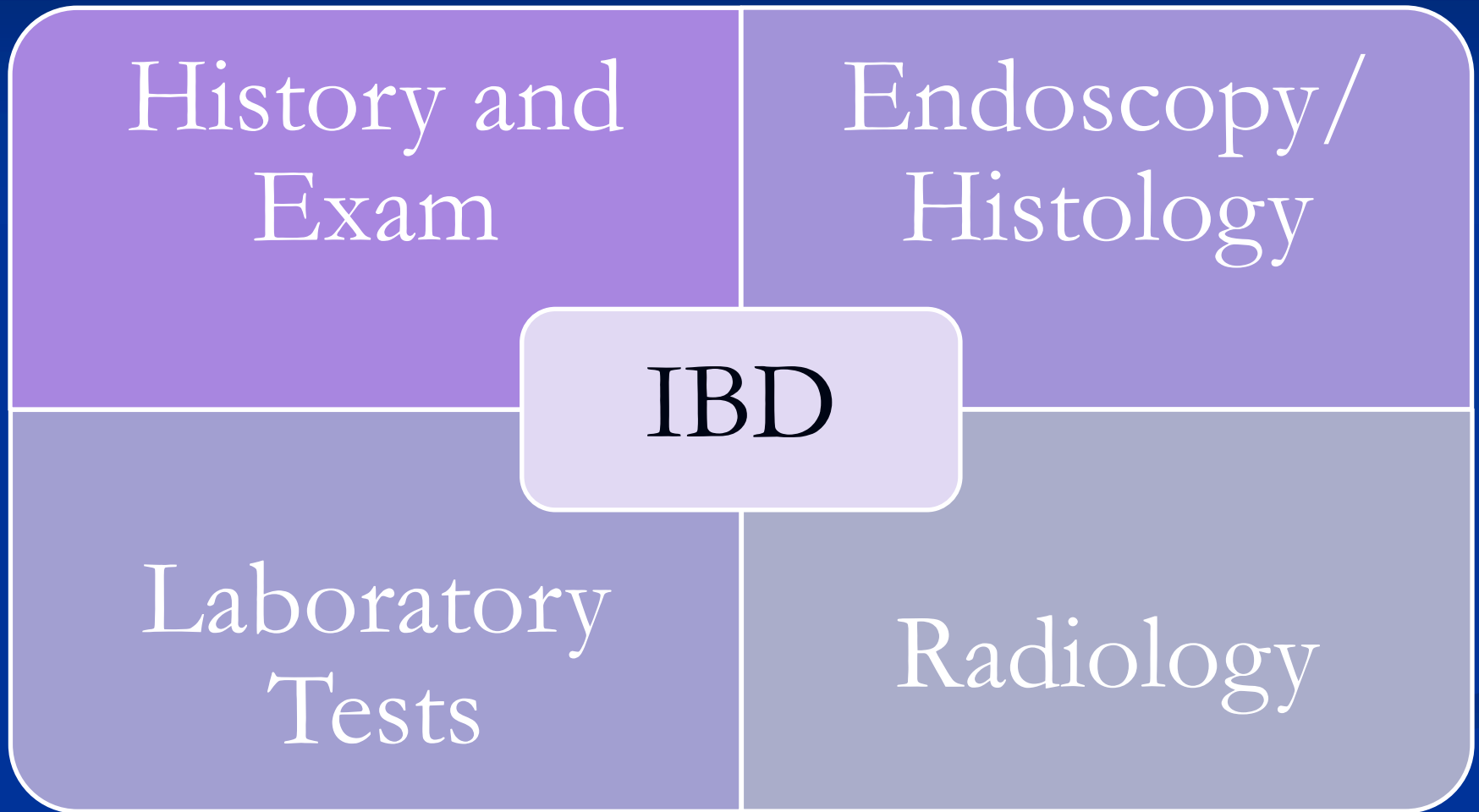


Abdominal Pain



How do we Diagnose IBD?

Diagnosis



Differential Diagnosis

- Infectious Diarrhea
- Medication induced colitis
- Celiac Disease
- Irritable Bowel Syndrome
- Lactose Intolerance
- Malignancy
- Ischemic colitis
- Diverticulitis
- Radiation Colitis
- Microscopic colitis
- Neuroendocrine tumors



Labs:

- Cmp
- Cbc
- C-Reactive Protein: Protein made in the liver when there is inflammation, infection, malignancy. More acute phase reactant
- ESR: Can reflect more long term inflammation
- Fecal calprotectin: Gold standard for inflammation in the GI tract

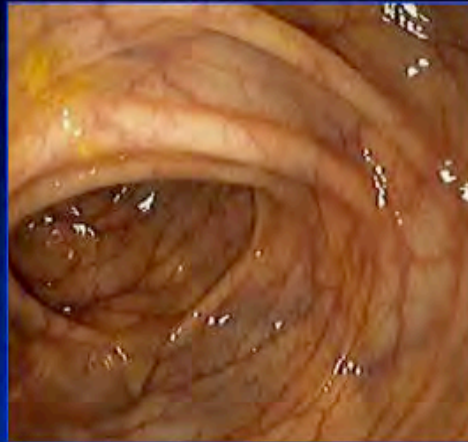
Labs:

- Vit B12
- Iron and Ferritin: iron and ferritin may be low with inflammation. Ferritin can also be elevated as acute phase reactant
- Vit D: vit d is anti inflammatory.
Recommended to supplement if low
- C. Diff (very common to get when pts have inflammation)

Endoscopic Findings in UC

UC - Spectrum of Disease

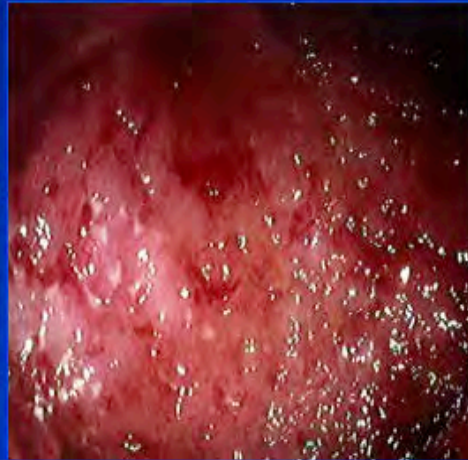
Normal



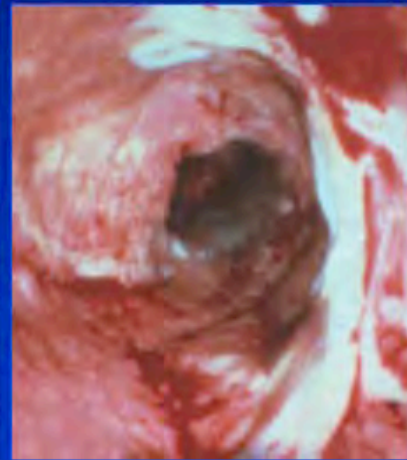
Mild



Moderate

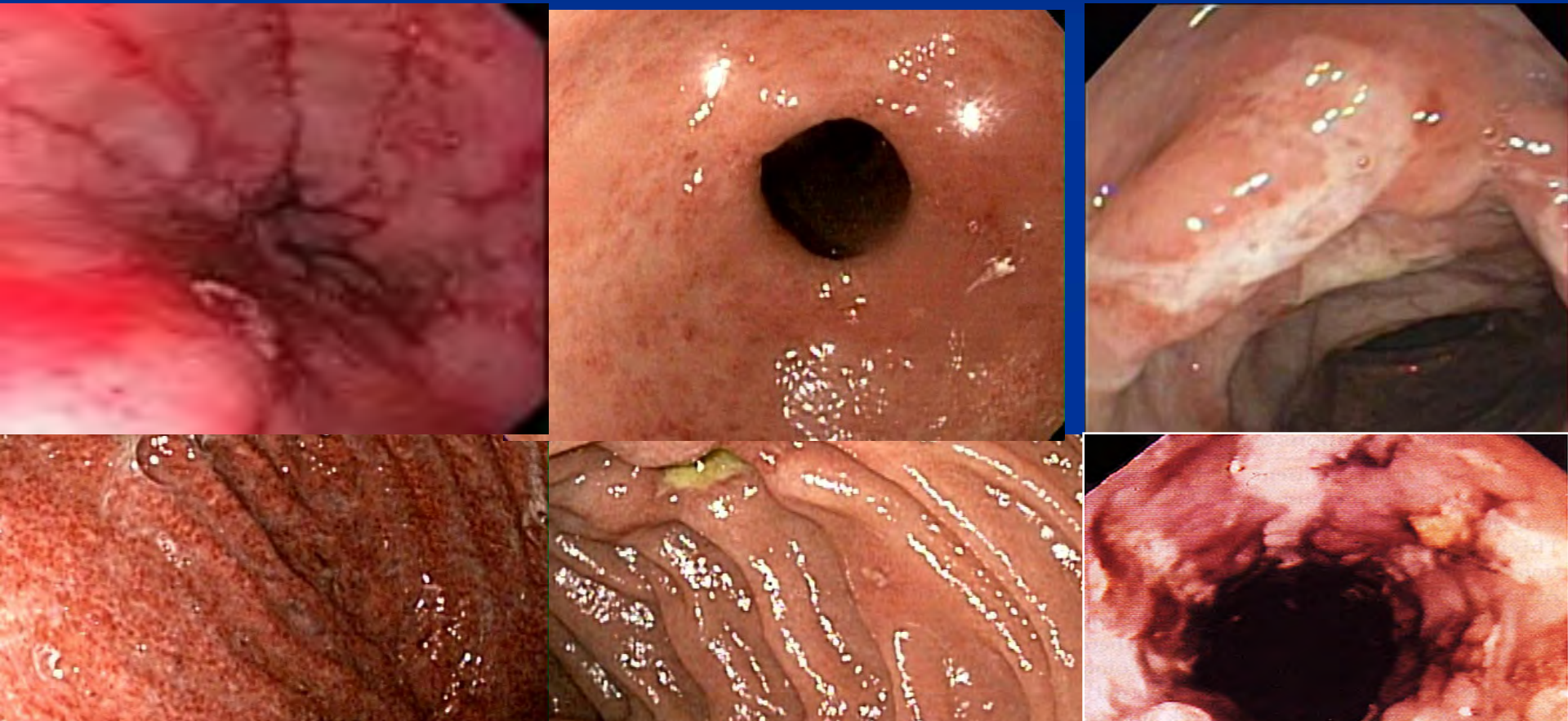


Severe

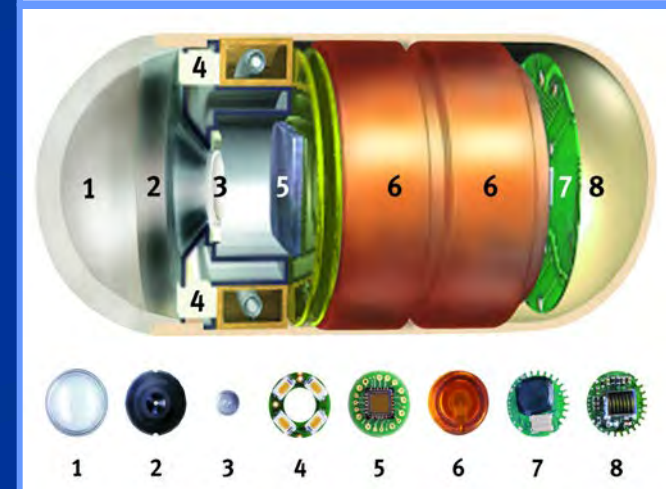
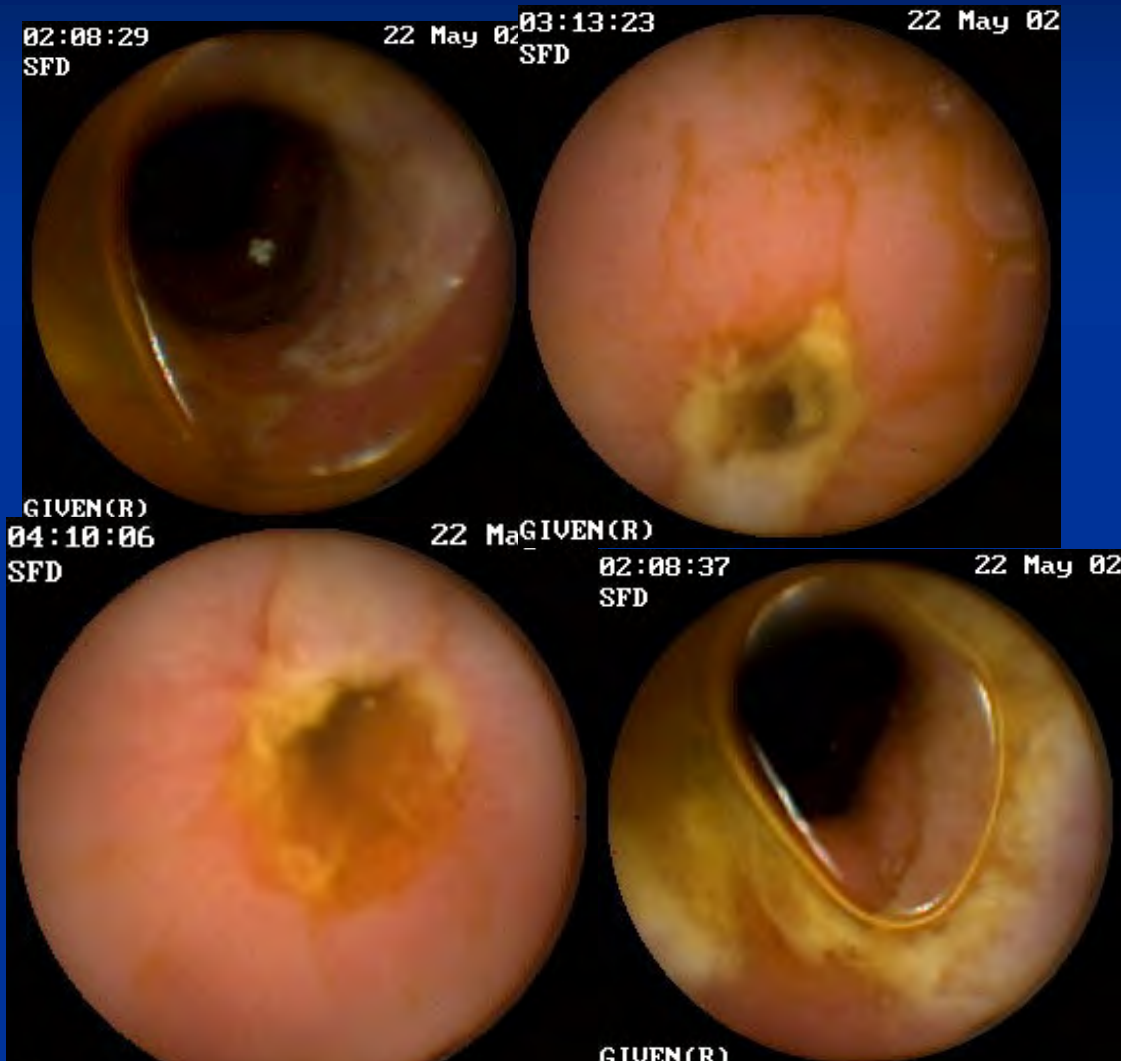


Crohn's Disease

Endoscopic Findings



Capsule Endoscopy

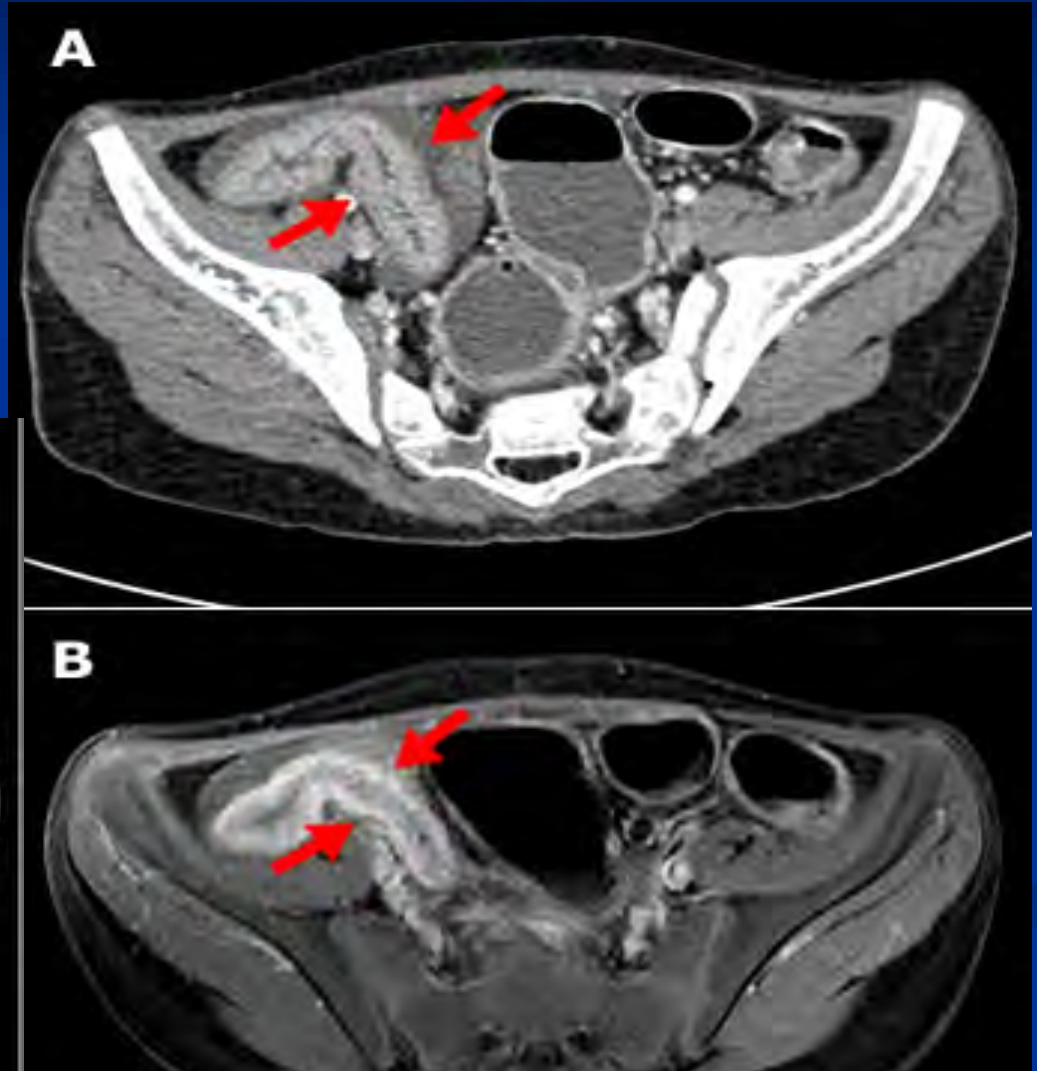


Capsule Endoscopy

- First introduced in 2000
- Indications: suspect ibd, assess small bowel disease in confirmed ibd pts; assess post operative recurrence
- If you suspect stricture, either get MRE or do patency capsule first.
- Results are very dependent on reader expertise

Radiology

- X-ray, CT, MRI
- CTE and MRE



Serologies

Test Result

<input checked="" type="checkbox"/> IBD Predicted <input type="checkbox"/> IBD Not Predicted	<table border="1"> <tr> <td colspan="2">PROMETHEUS IBD Serology 7</td><td>IBD</td><td>CD</td><td>UC</td></tr> <tr> <td colspan="2">Overall Performance</td><td>Sensitivity</td><td>93%</td><td>88%</td><td>93%</td></tr> <tr> <td colspan="2"></td><td>Specificity</td><td>95%</td><td>98%</td><td>97%</td></tr> <tr> <td colspan="2"></td><td>PPV</td><td>96%</td><td>96%</td><td>89%</td></tr> <tr> <td colspan="2"></td><td>NPV</td><td>90%</td><td>93%</td><td>98%</td></tr> </table>	PROMETHEUS IBD Serology 7		IBD	CD	UC	Overall Performance		Sensitivity	93%	88%	93%			Specificity	95%	98%	97%			PPV	96%	96%	89%			NPV	90%	93%	98%
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		NPV	90%	93%	98%																									
<input type="checkbox"/> Ulcerative Colitis Predicted <input checked="" type="checkbox"/> Crohn's Disease Predicted	<p>PROMETHEUS™ Predictive Algorithm Description:</p> <ul style="list-style-type: none"> Utilizes Smart Diagnostic Algorithm (SDA) technology to characterize complex relationships between multiple markers to produce a diagnostic prediction with greater accuracy than simple comparison of assay results to a reference range. Developed (n=1813; 36% CD, 24% UC, 20% IBS, 20% normal) and validated (n=500; 38% CD, 21% UC, 41% normal) using serology results for samples with a known diagnosis. 																													

Assay Information

Assay	ASCA IgA ELISA	ASCA IgG ELISA	Anti-OmpC IgA ELISA	Anti-CBir1 ELISA	Neutrophil-Specific Nuclear AutoAntibodies (NSNA) (IBD specific pANCA)		
					AutoAntibody ELISA	IFA Perinuclear Pattern	DNase Sensitivity
Assay Value	109.4 EU/ml	113.8 EU/ml	26.0 EU/ml	50.2 EU/ml	< 12.1 EU/ml	Not Detected	Not Detected
Note: Test result determined by the PROMETHEUS Predictive Algorithm without direct consideration of assay values relative to reference values. However, interpretation of prognostic information should be made based on relative differences between assay values and reference values.							
Reference Value	< 20.0 EU/ml	< 40.0 EU/ml	< 18.5 EU/ml	< 21.0 EU/ml	< 12.1 EU/ml	Not Detected	Not Detected



Serum Markers for IBD

Marker	Prevalence
ASCA (or other anti-glycans)	35%–76% of CD patients ^{1,6}
pANCA	30%–83% of UC patients ¹
IBD-specific (DNase) pANCA*	10%–25% of CD patients ^{1,2} 40%–60% of UC patients ^{1,2}
Anti-CBir1*	50%–55% of CD patients ⁴
Anti-OmpC*	55% of CD patients ³
Anti-I2*	54% of CD patients ⁵

1. Sandborn WJ. *Rev Gastroenterol Disord.* 2004;4:167-74.

2. Vidrich A, et al. *J Clin Immunol.* 1995;15(6):293-9.

3. Landers CJ, et al. *Gastroenterology.* 2002;123:689–99.

4. Targan SR, et al. *Gastroenterology.* 2005;128:2020-8

5. Sutton CL, et al. *Gastroenterology.* 2000;119:23-31

5. Dotan, I., et al. *Gastroenterology*, 2006;131:366-378

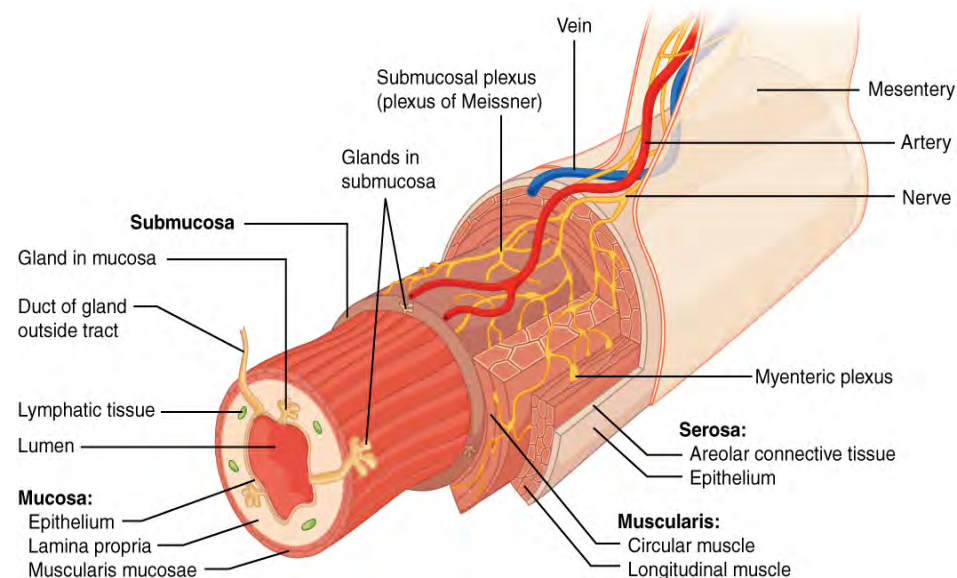
Genetic Markers in CD: NOD2

- ❖ *NOD2/CARD15*
 - ❖ First IBD susceptibility gene identified in 2001^{1,2}
 - ❖ Genetic risk factor associated with CD
 - ❖ Only genetic marker commercially available for CD
 - ❖ NOD2 mutations are associated with younger age of onset, small bowel involvement and stricturing disorder
 - ❖ 1 copy of mutated gene = 1.5 – 4 x risk
 - ❖ 2 copies of mutated gene = 15 – 40 x risk
- ❖ Currently there about 240 genetic variants related to ibd

1. Hugot J, et al. *Nature*. 2001;411:599-603.
2. Ogura Y, et al. *Nature*. 2001;411:603-6.
3. Abreu MT, et al. *Gastroenterology*. 2002;123:679-88.

What is Crohn's Disease

- Crohn's Disease is a non curable, idiopathic, chronic, transmural inflammatory autoimmune disease that can affect the GI tract from mouth to anus
- There are 4 layers to the Gi Tract:
 1. Mucosa
 2. Submucosa
 3. Muscularis
 4. Serosa
- Transmural inflammation affects all 4 layers which result in the complications we may see in CD



CROHN'S DISEASE

Disease Location at time of Diagnosis:

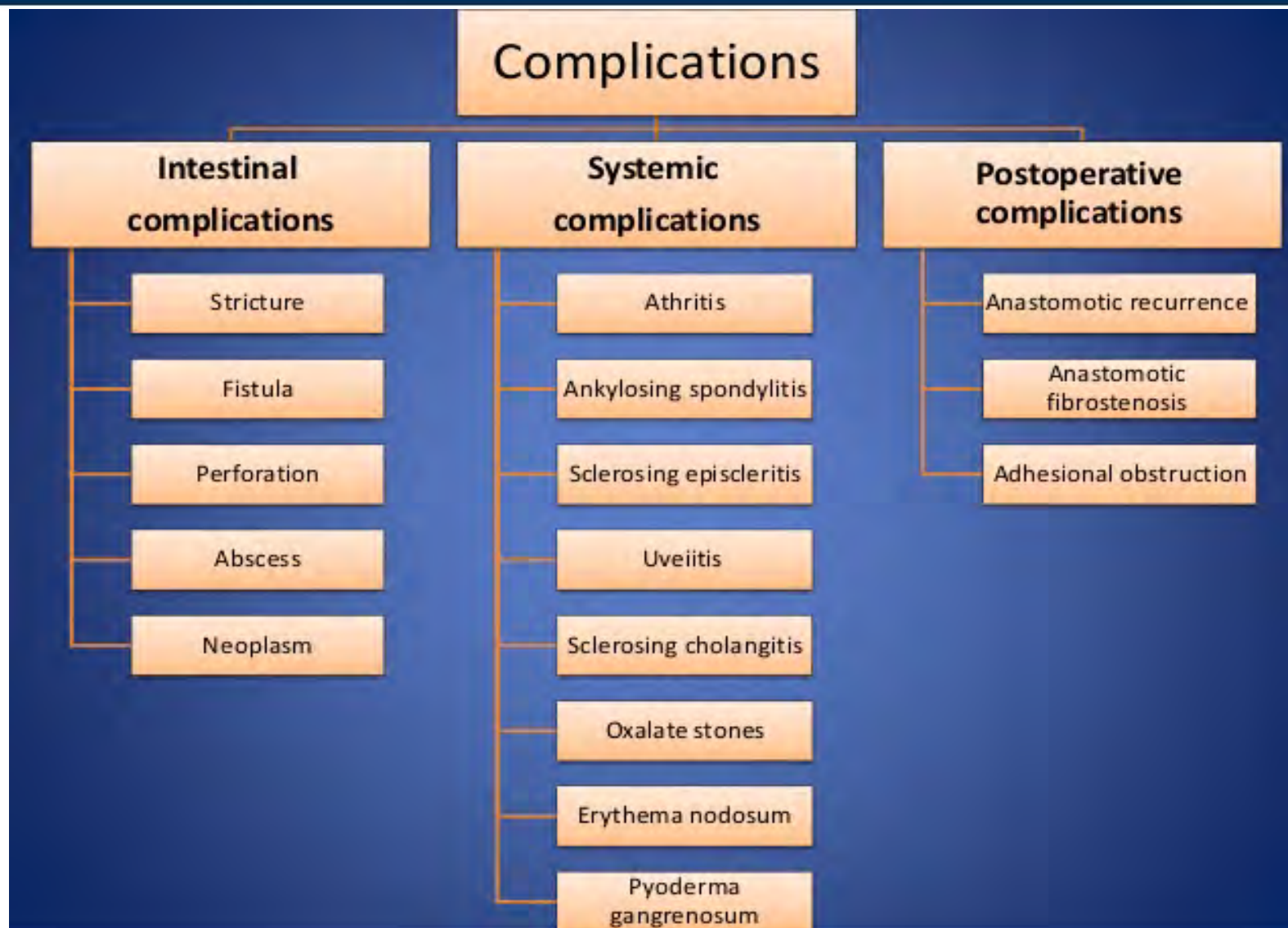
1. 44.8% Terminal ileum
 2. 26.7 % Isolate colon (1/3 of pts will have perianal disease)
 3. 24.2% ileocolonic
 4. 4.3% Upper GI
- The site of Disease, small intestine or colon, tends to remain stable over time with 6% - 14% having a change in disease locations over time.

Hamon JF et al. Ann Gastro Hep. 1993
Peschard S et al. Gastroenterol Clin Biol 1993
Louis E et al. Gut 2001
Lichenstein et al. ACG Guidelines. April 2018.

Hendrickson, et al. Clinical Microbiology Reviews 2002; 15(1): 79-94

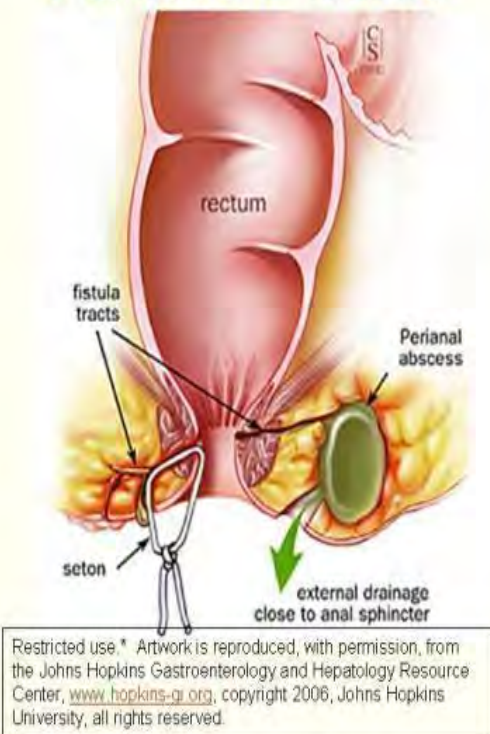


Complications of Crohn's Disease



Perianal disease in Crohn's

Perianal Disease



32

(c) 2007, Laurence S. Bailen, MD

- ❖ The lifetime risk of developing a fistula in patients with Crohn's ranges from 20-40 % (1)
- ❖ The cumulative frequency of fistula occurrence was 12% at 1 year, 21% at 10 years and 26% at 20 years (2)

1. Sandborn WJ, Fazio VW, Feagan BG et al. AGA technical review on perianal Crohn's disease. *Gastroenterology* 2003;125:1508–30
2. Langholz, Ebbe. Current Trends in Inflammatory Bowel Disease. *Therap Adv Gastroenterol*. Mar 2010; 3(2): 77–86

Rectal Abscess

- Abscess are very painful (perianal swelling, induration and fluctuation)
- Can be low (intersphincteric, perianal, ischiorectal)
- Can be high (submucosal, supralelevator)
- DX: Physical Exam (painful, fluctuance, tenderness), EUA, and imaging



Abcarian H. Anorectal Infection: Abscess-Fistula. Clin Colon Rectal Surg. 2011 March 24(1): 14 -21
Ghahramani L, et al. Antibiotic therapy for prevention of fistula in –ano after incision and drainage of simple perianal abscess: A randomized single blind clinical trial. Surgery. 2017 (Nov; 162(5): 1017 - 1025

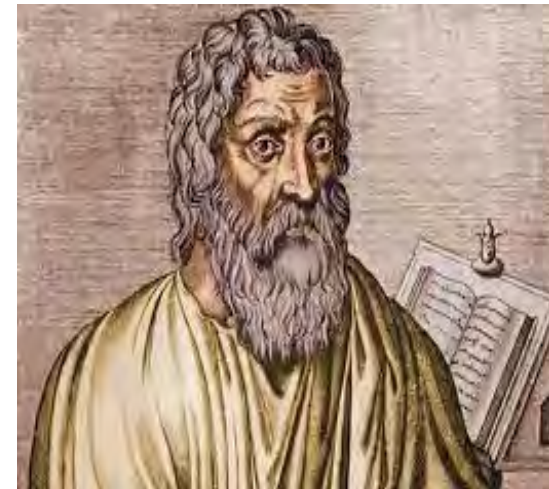
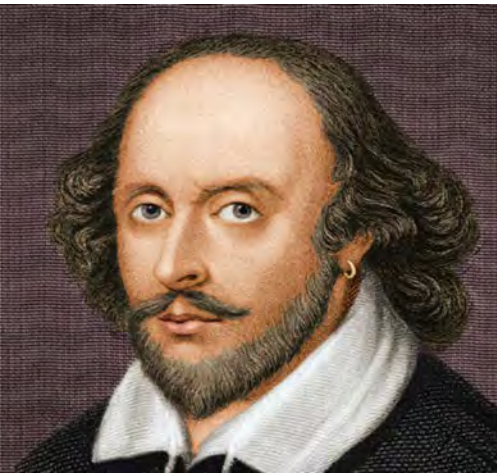
Anal Abscess:

- Priority: Draining the abscess (I&D). Antibiotics alone not enough because the wall of the abscess has necrotic and occluded blood vessels, so antibiotics won't penetrate
- If the abscess does not heal alone in 2 – 3 months, you should suspect a fistula
- Should antibiotics be used after I&D of abscess? Study done of 307 patients determined that a course of antibiotics like cipro and flagyl for 7 – 10 days is helpful in preventing fistula formation post I&D.

Abcarian H. Anorectal Infection: Abscess-Fistula. Clin Colon Rectal Surg. 2011 March 24(1): 14 -21
Ghahramani L, et al. Antibiotic therapy for prevention of fistula in –ano after incision and drainage of simple perianal abscess: A randomized single blind clinical trial. Surgery. 2017 (Nov; 162(5): 1017 - 1025

Peri Anal Fistula History

- William Shakespeare's Comedy All's Well That Ends Well written in 1603 uses a cure for fistula as a central plot (Cosman BD. DCR 1998;41;914 – 924)
- Hippocrates (460-357 BC) made reference to surgical treatment of Anal Fistula



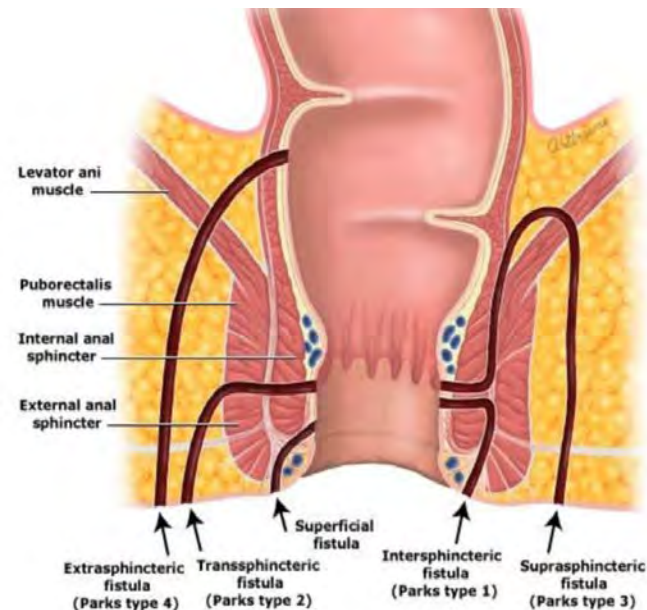
Perianal Fistula



Diagnosis of Anal Fistulas

- Obtain imaging to study anatomy, assess for abscess and infection.
- MRI: diagnostic specificity 76 – 100%
- EUS: In a study of 90 patients, 95% of fistulas were identified by EUS which coincided with surgical findings in 85 percent of patients, and chronic fistula cavities were confirmed by surgery in 75 percent of patients. (Limitation is the Interventionalist experience.)
- Endoscopic exam under Anesthesia: typically done by a Surgeon in the OR.
- EUA procedures including abscess drainage, seton placement and fistulotomy can be done.
- Accuracies of diagnosis complex perianal disease was 87% (MRI), 91% (EUS) and 91% (EUA)

Management of Anal Fistulas



AGA distinguishes between simple and complex.

- Simple fistulas are low and include superficial, intersphincteric or intrasphincteric below the dentate line, with 1 opening and no complications, and involved <0
 - Heal better than complex fistulas (88.2% vs 64.6%)
- Complex fistulas are high and include intersphincteric, transsphincteric, extrasphincteric, suprasphincteric, above dentate line, with many external openings and associated with complications (abscess, rectal stricture, connection to bladder to vagina), and involve >30% of the external sphincter.
 - Have higher rates of recurrence than Simple Fistulas (41.9% vs 26.7%)
 - Regarding Surgical Outcomes they are higher to end up needing permanent fecal diversion (63.5% vs 26.7%)

Park's Classification

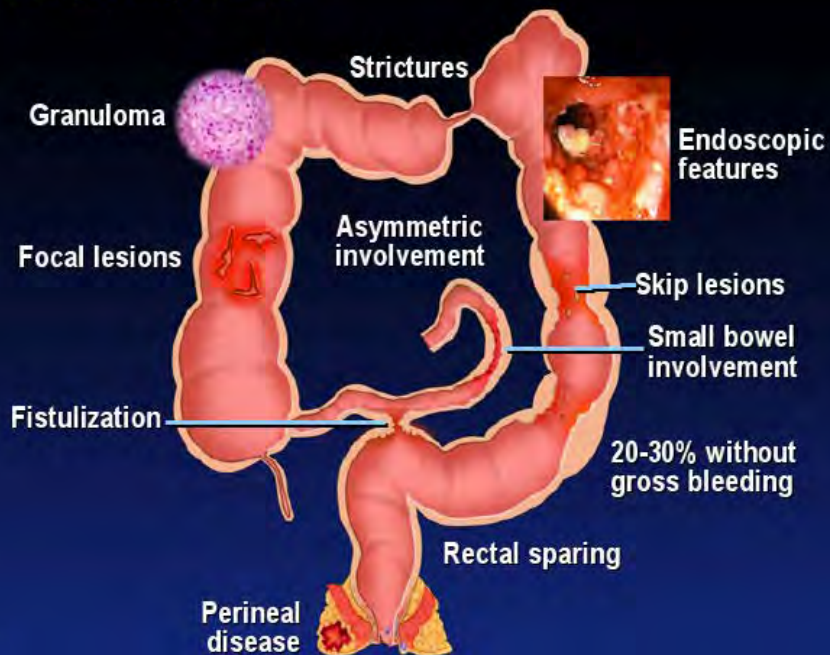
Castro LA et al. Ann Gastroenterol. 2017;30 (1) 33-44.

Treatment of Perianal Fistula

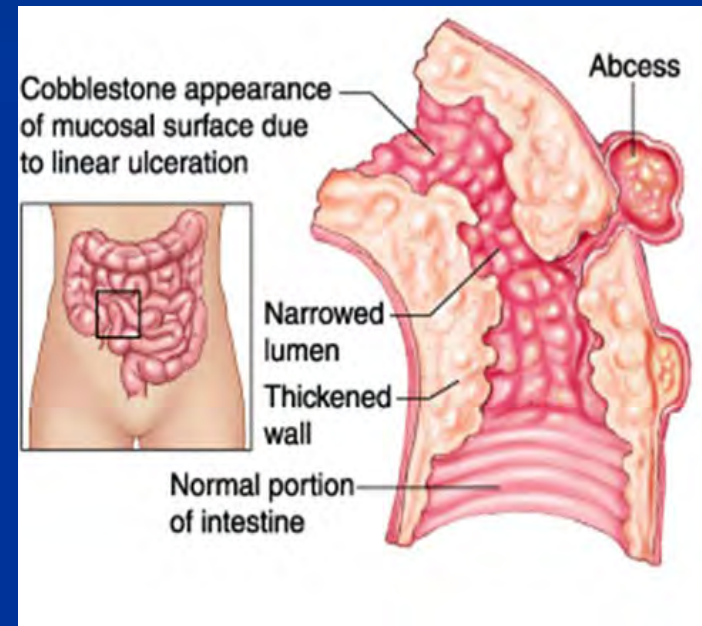
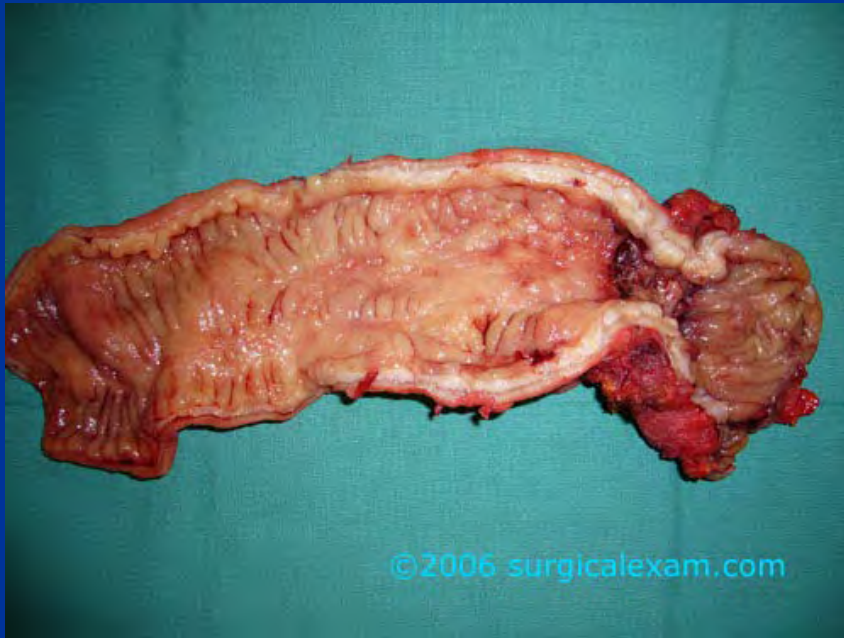
- Antibiotics:
 - Ciprofloxacin and metronidazole
 - Augmentin can be used;
 - IV Antibiotics for sepsis
- I & D of abscess
- Steroids do not show efficacy and should be avoided.
- **Coordinate care with surgeon**
- **Best treatment if combination medical and surgical therapies**

Strictures

CD - Distinguishing Features



Stricture in Crohn's



Stricturoplasty

Indications

- Diffuse small bowel involvement with multiple, short fibrotic strictures
- Hx of extensive small resection
- Rapid, symptomatic recurrence of stricture w/in 1year
- Isolated ileocolonic anastomotic stricture
- Reserved for small bowel stricture not colonic

Contraindications

- Abdominal Sepsis (phlegmon)
- Suspicion of Cancer
- Poor nutrition
- Macroscopic active disease at stricture site is not contraindication

Strictureplasty



Strictureplasty



Strictureplasty

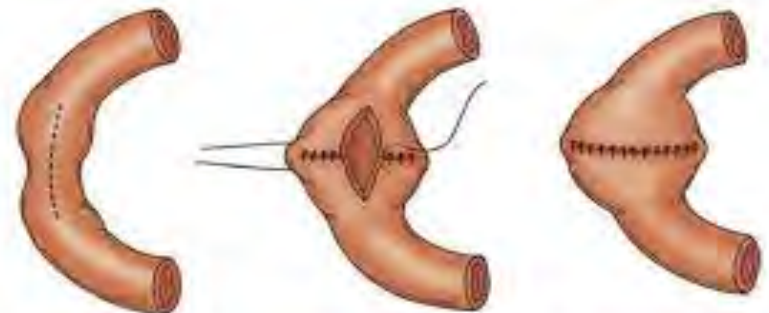
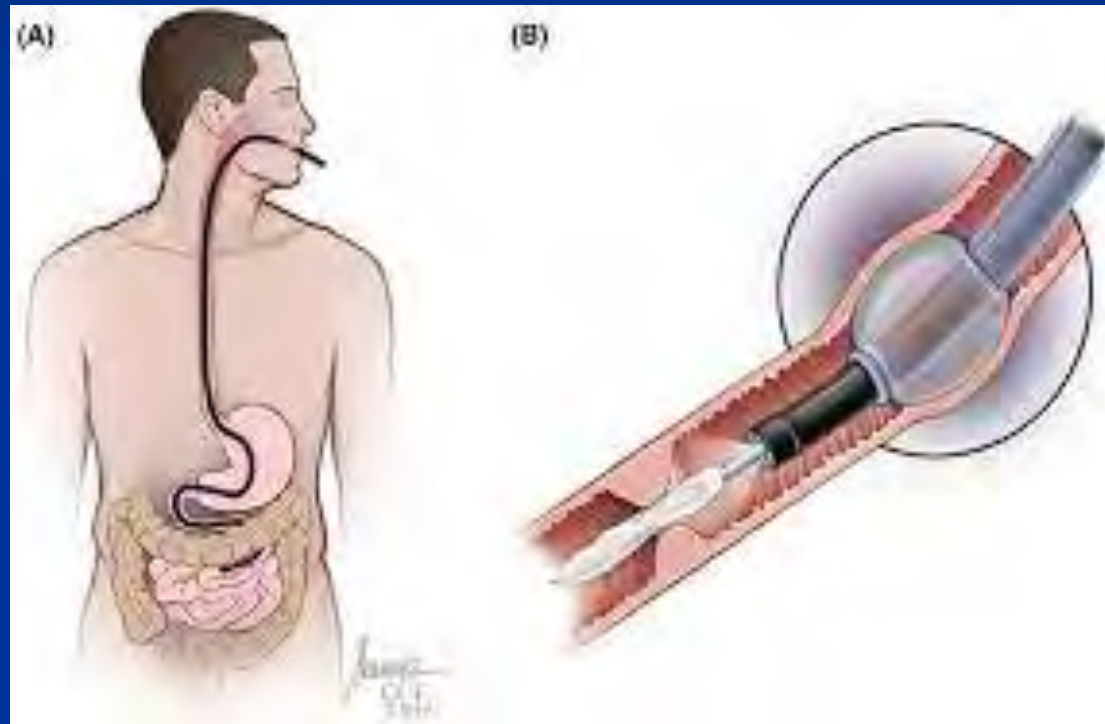


FIG. 1 Heineke-Mikulicz strictureplasty on an isolated stricture. A single-layer everting technique is performed to close the longitudinal enterotomy transversely, reconstructing an unobstructed lumen.

Balloon Dilation of Small Bowel Stricture

- An alternative to surgery
- Study done of 95 pts:
 - Short term symptomatic relief: 66 pt (69.5%)
 - Procedure failure: 6 pt (6.3%)
 - Adverse reaction: 5 pt (5%)
- Works best for short segment stricture: <5
- Coordination of care with Interventionalist

Endoscopic Balloon Dilation



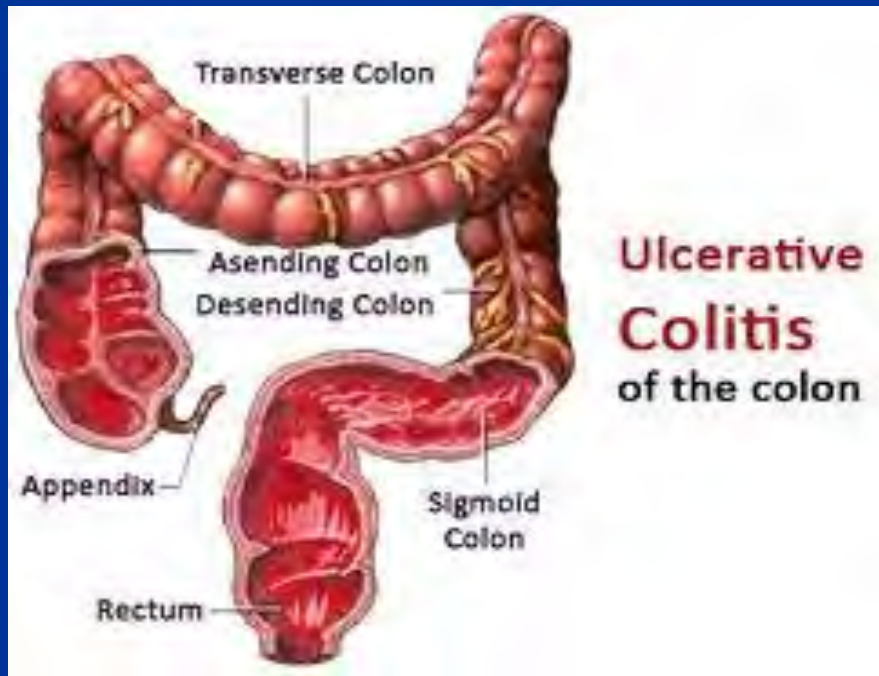
Surgery for Small Bowel CD

- Laparoscopic Surgery is the best
 - Resection
 - Ileocectomy
- Two RCT 120 pts
- Lap surgery associated with less wound infection
- Lap surgery reduced re-operation rates and complications

CONCLUSION: LAPAROSCOPIC SURGERY SAFE AS OPEN

Ulcerative Colitis

Superficial inflammation



Extent of disease

- ❖ Inflammation occurs in the rectum and extends continuously proximally
- ❖ •“Extensive disease” involves the colon beyond the splenic flexure
- ❖ •“Pancolitis” involves the entire colon
- ❖ •Proctitis is initially diagnosed in 30-50% of adults, with approximately half developing more extensive disease over time

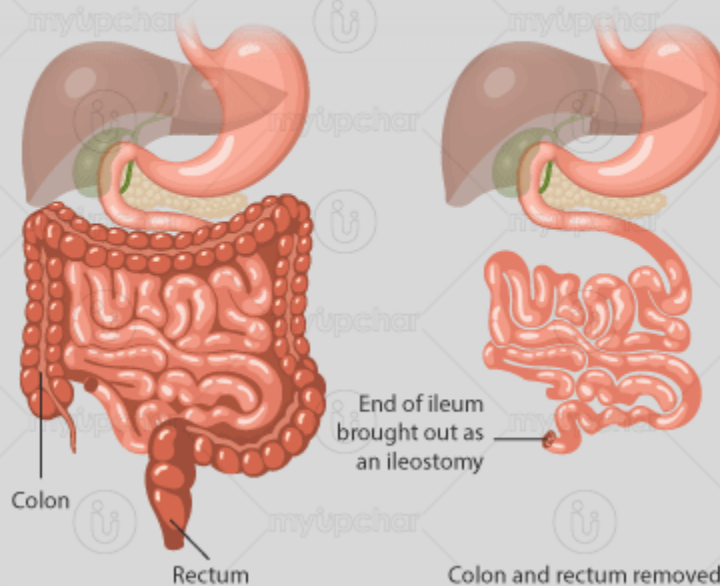
Surgery for UC

- Total Proctocolectomy: removal of total colon and anus
- You cannot remove it by parts only
- Can be followed by an Ileal Pouch-Anal Anastomosis (IPAA)

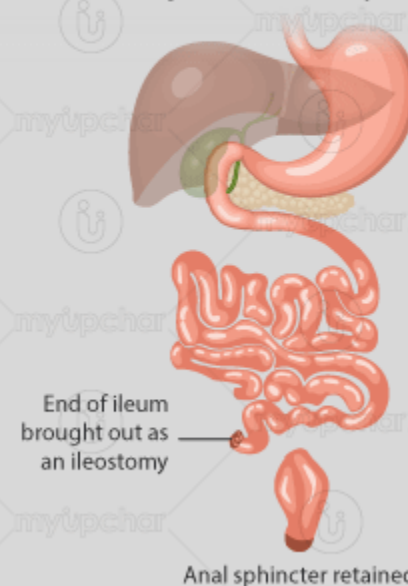
Proctocolectomy



Total proctocolectomy

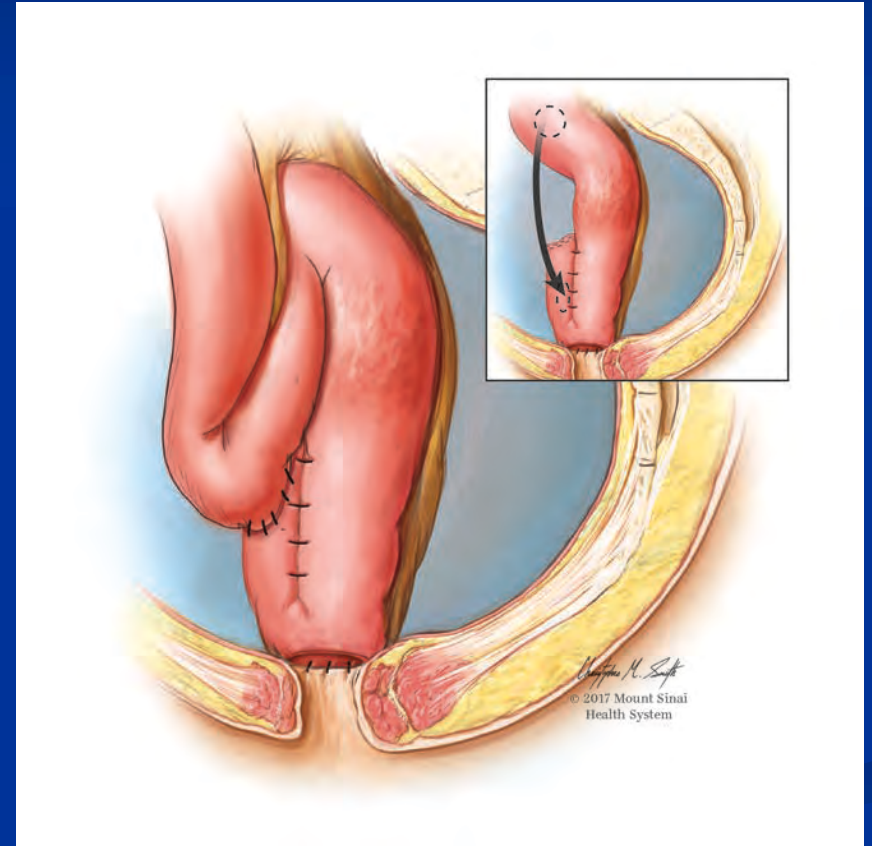


Restorative proctocolectomy



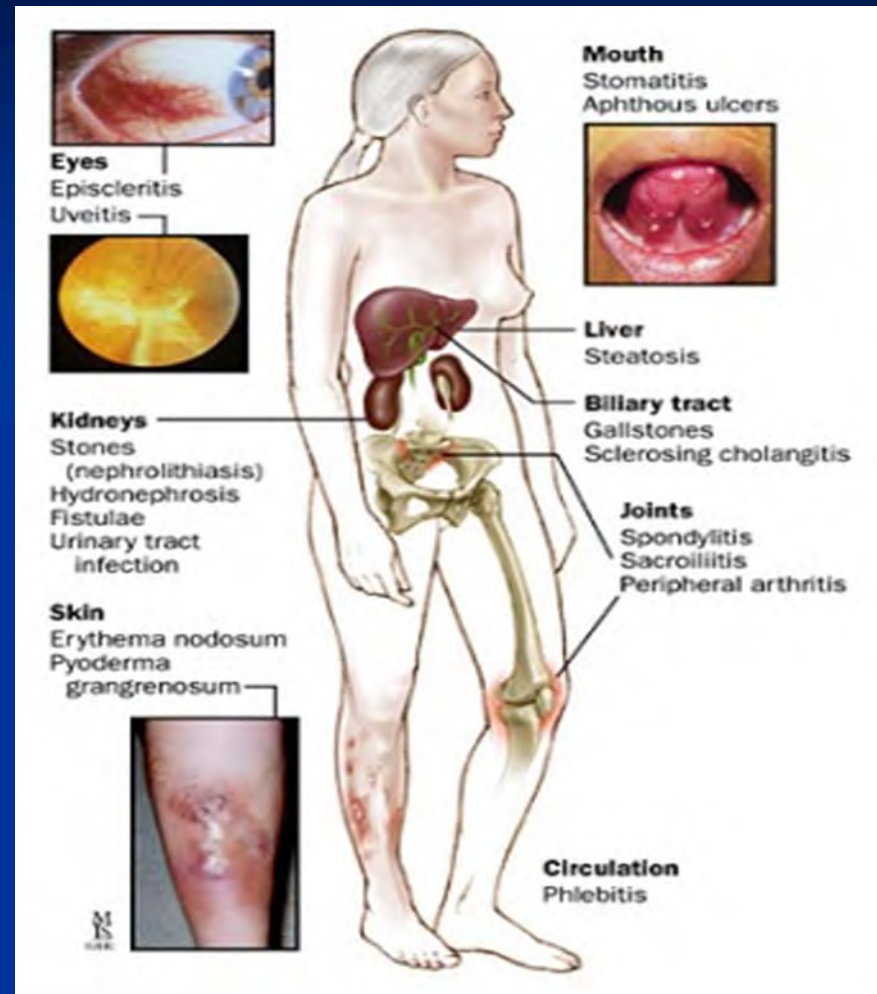
J Pouch

- With a J pouch, pts will have between 4 – 8 bowel movements a day
- There are potential complications such as pouchitis (worse diarrhea, bleeding, pain)
- 10% of patients may develop Crohn's Disease in the pouch



Systemic Complications of the IBD

- ❖ Up to 36% of patients with IBD will develop an extra intestinal manifestation
- ❖ Occurs in up to 15% of patients with CD and about 10% of patients with UC
- ❖ PG is an ulcerative neutrophilic dermatosis seen in only 1–5% of IBD patients.
- ❖ Uveitis and episcleritis occurs in 4 – 12% of UC and Crohn's patients.



Primary Sclerosis Cholangitis

- The prevalence of IBD in pts with PSC approaches 90%
- UC pts have a 5% chance of having PSC
- CD pts is less at 1%
- Patients with both IBD and PSC have a higher risk of Colon Cancer than just having IBD alone
- AGA and ACG guidelines recommend colonoscopy annually in concomitant PSC and IBD patients.
- Patients with PSC should be followed regularly with a Hepatologist.

GOAL OF THERAPY



**DON'T JUST
TREAT GI
SYMPTOM!**



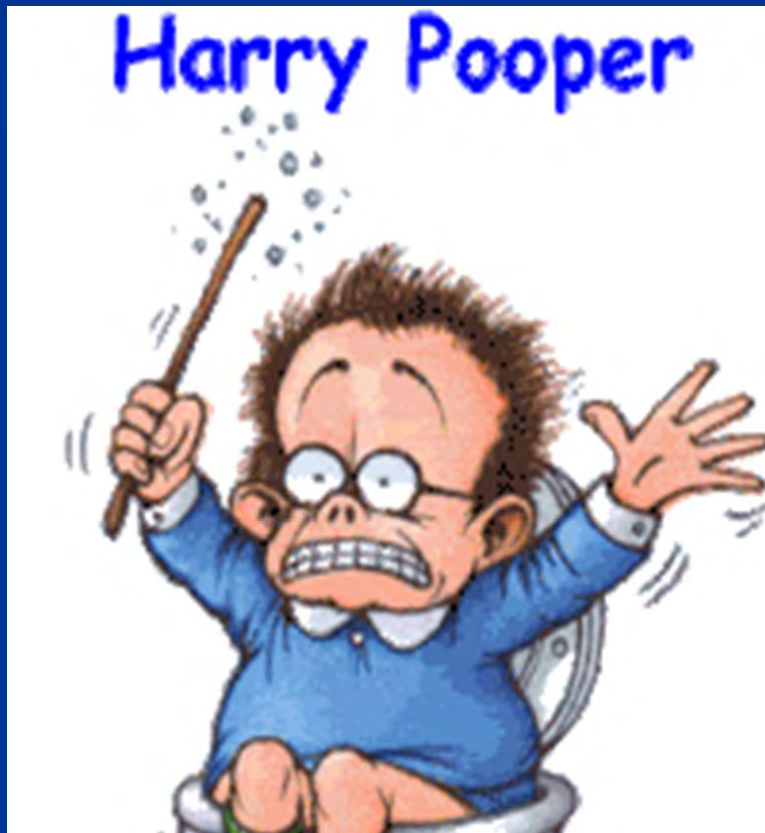
Our true goal should
be overall health and
wellness



- Goal of Treatment is Deep Remission:
 - Clinical Remission
 - Endoscopic healing of mucosa

Goal is for patients experience in the bathroom to go:

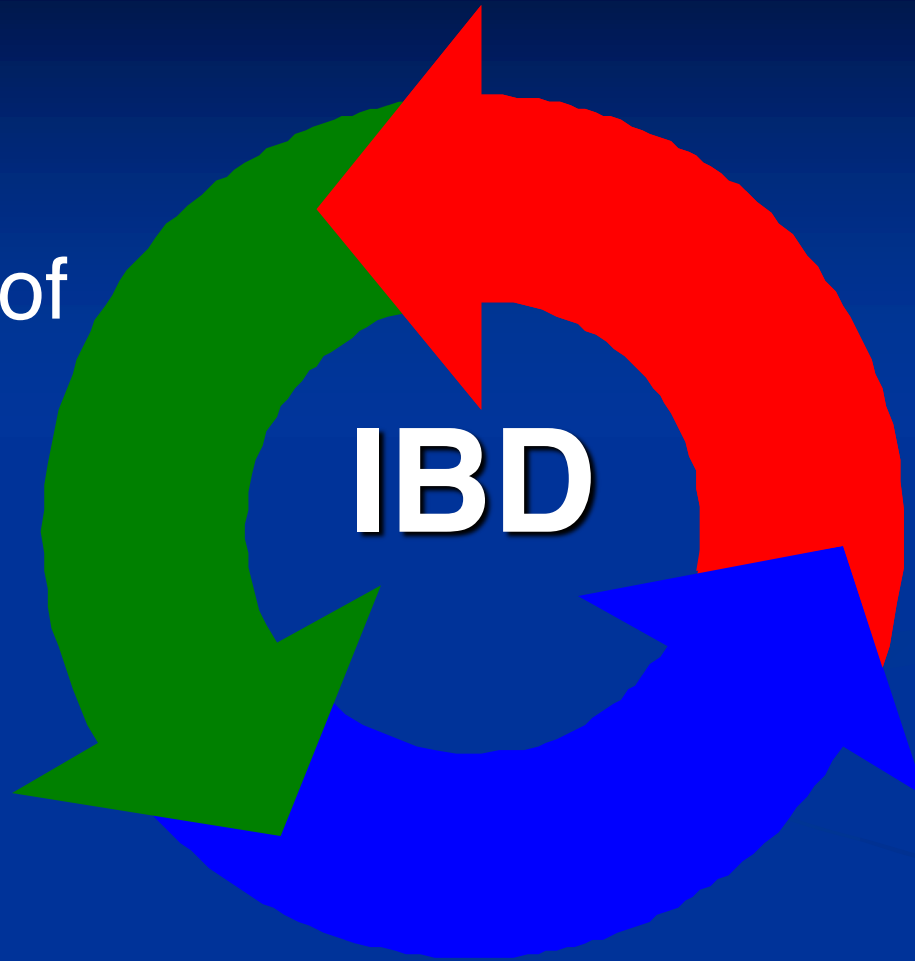
From this



To this



Induction of
remission



Maintenance
of remission
off steroids
and/or
Mucosal
healing
(histology)

Maintenance of
remission

Picking therapy based on patient

Symptoms

Mild—bothered but
functions at a normal
capacity

Moderate (affects daily life)

Severe (close to or needing
hospitalization)

Severity of Inflammation

Superficial ulcerations

Deep
ulcerations/inflamma-tory
stricture

Fibrotic stricture

Internal perforating disease
(+/- abscess)

Perianal perforating

Location

Limited ileal disease

Extensive small bowel
involvement

Extensive colonic
involvement

Rectal disease

IBD Therapies :

Help is on the way!!

- Antibiotics
- Steroids
- Mesalamines
- Immunomodulators
- Biologics:
 - Anti TNF
 - Anti Integrins
 - Interleukin Blocker
 - JAK kinase inhibitors
 - New Therapies in pipeline



Antibiotics

■ Ciprofloxacin and Flagyl

-Typically used currently for the treatment of abscesses and perianal fistulas in Crohn's disease

Steroids

- Induce the apoptosis of lymphocytes and alter leukocyte migration and redistribution
- Inhibit cytokine gene expression, resulting in a decreased release of interleukins (IL), interferons (IFN) and tumor necrosis factor (TNF), such as IL-2, IL-6, IFN- γ and TNF- α , While the simplest mechanism of negative

Steroids

- Prednisone
- Budesonide (Entocort and Uceris)
- Hydrocortisone enemas
- Uceris foam
- Cortifoam

**NOT THE GOAL OF
STEROIDS!!!!**



STEROIDS

i think this guy might have taken some

BUDESONIDE

Uceris™ : MMX® Technology Allows Budesonide to Target the Full Length of the Colon

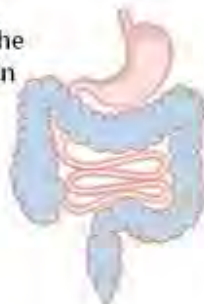
Uceris (budesonide)

Uceris is indicated for the induction of remission in patients with active, mild to moderate UC

Target:
Full length of colon

MMX technology:
Pill dissolves at pH ≥ 7.0 , the approximate pH level near the entry to the colon

Dosage:
9 mg tablet QD



Uceris, unlike Entocort® EC, is designed for targeted local action at the entire site of UC

Entocort® EC (budesonide)

Entocort® EC is indicated for the treatment of active, mild to moderate Crohn's disease involving the ileum and/or ascending colon

Target:
Ileum/ascending colon

Controlled ileal release:
Pill dissolves at pH > 5.5 the approximate pH level of the duodenum

Dosage:
3 mg x 3 capsules QD



Steroids

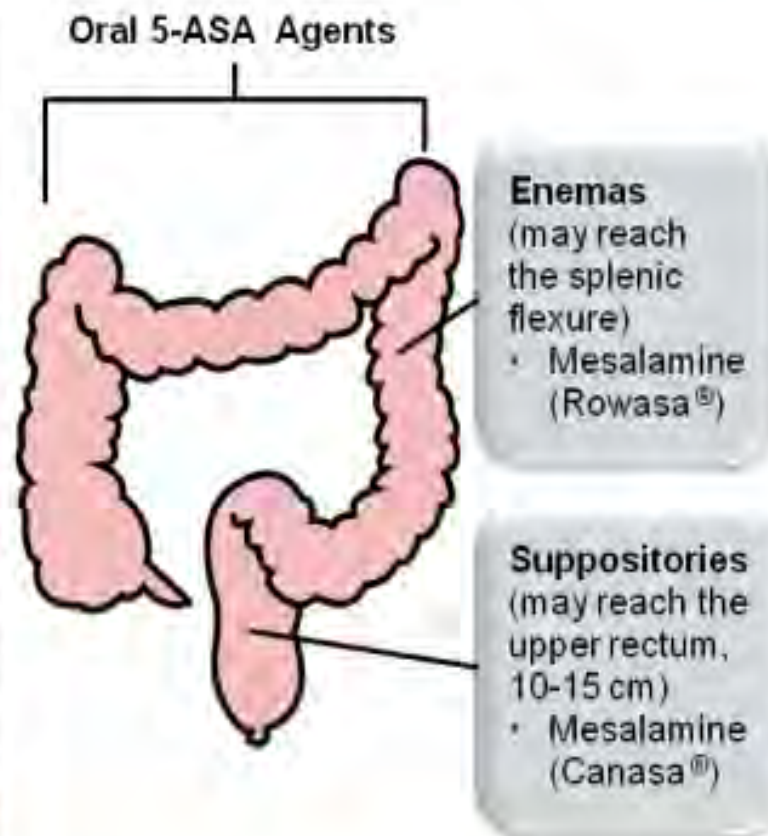
Event	Estimated Frequency
Any side effect leading to the d/c of prednisone	55%
Ankle swelling	11%
Facial swelling	35%
Easy bruising	7%
Acne	50%
Memory problems	7%
Psychosis	1%
Infections	13%
Cataracts	9%
Increased intraocular pressure	22%
HTN	13%
Osteoporosis	33%
Diabetes	10 X increased risk

Mesalamines/5-ASA

- Mainstay therapy for mild to moderate UC is sulfasalazine and other 5 ASA agents. Effective in inducing and maintaining remission in UC. Limited role in CD
- Mechanism of Action:
 - Exerts local anti inflammatory effects likely by blocking cyclooxygenase and inhibiting prostaglandin production in the colon
 - Newer formulations deliver active ingredient to different sites of colon and thus limit toxicity
 - Topical therapies including suppositories and enemas exist

5-ASA agents and location of action

Mesalamine	
Asacol [®] /Asacol [®] HD	delayed release, pH dependent
Pentasa [®]	controlled release via ethyl cellulose
Apriso [®]	delayed release, pH dependent, extended-release matrix core
Lialda [®]	multi-matrix system (MMX), pH dependent
Olsalazine	
Dipentum [®]	azo-bonded pro-drug activated by bacteria
Sulfasalazine	5-ASA linked to sulfapyridine by azo-bond
Balsalazide	
Colazol [®]	azo-bonded pro-drug activated by bacteria



This rectum is so inflamed it's untamed!

inflamed-and-untamed.com



Look at all
this
inflammation

Using mesalamine
enemas allows you to
put medication directly
into the rectum where
the inflammation is
located.



Adverse Effects Associated With Oral 5-ASAs

Sulfasalazine

- Headache
- Nausea/vomiting
- Dyspepsia
- Anorexia
- Rash
- Bone marrow suppression
- Interstitial nephritis
- Megaloblastic anemia
- Apparently reversible oligospermia
- Folate malabsorption
- Connective tissue disease
- Pancreatitis
- Pericarditis
- Hepatitis
- Paradoxical exacerbation of colitis

Olsalazine, Balsalazide, Mesalamine

- Headache
- Nausea
- Rash
- Hair loss
- Interstitial nephritis
- Pericarditis
- Pneumonitis
- Hepatitis
- Pancreatitis
- Paradoxical exacerbation of colitis
- Secretory diarrhea (olsalazine)

Kornbluth A, Sachar DB. *Am J Gastroenterol*. 2010;105:501.

Sands B. *Gastroenterology*. 2000;118:S68.

Azulfidine (sulfasalazine) [package insert]. New York, NY: Pfizer; August 2006.

IMMUNOMODULATORS:

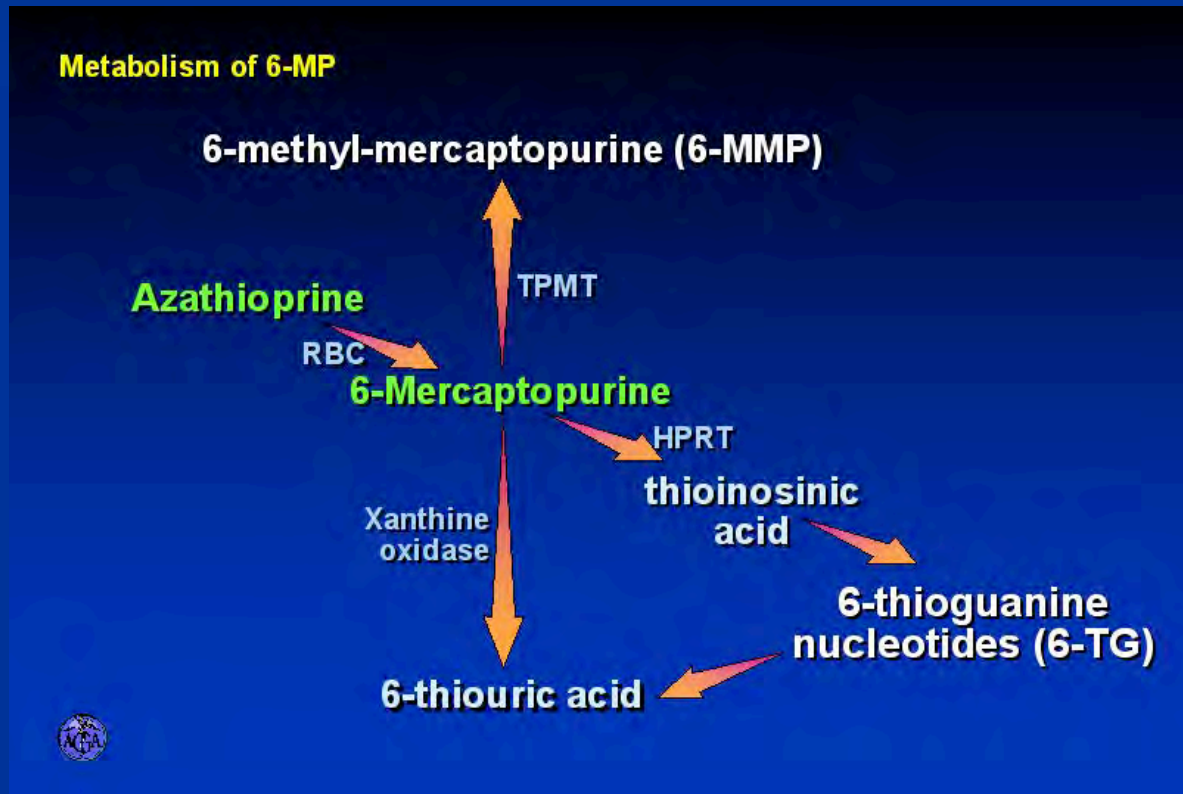
6mp and methotrexate

■ 6mp/Azathioprine:

- The thiopurines are immunosuppressive drugs that function by deactivating key processes in T lymphocytes that lead to inflammation
- Azathioprine is converted into the active form of 6mp
- Indicated for treatment of Crohns and UC with remission rates at about 20%
- Also indicated for immunogenicity
- Takes about 3 months to work

Immunomodulator Drugs

■ Azathioprine/6-MP



Azathioprine Risks

- BM – Leukopenia (2-5%)
- Hepatotoxicity (rare)
- Pancreatitis (3%)
- Drug intolerance (10-15%)
 - Fatigue
 - Nausea
 - Flu-like
 - Hypersensitivity rxn
- Infection (2-3:1)
 - Viral- HSV, CMV, EBV
- Lymphoma (~4x)

Methotrexate

- Indicated for the treatment of Crohns
- Has no data support use in the treatment of UC
- Mechanism of action:
 - Inhibits dihydrofolate reductase – a critical enzyme for the synthesis of thymidine & purines. At the low doses used for treatment of inflammatory bowel disease methotrexate's antiproliferative effects (that are observed in higher doses used to treat cancer) may not be evident.
 - Must avoid pregnancy
 - Also used as dual therapy for immunogenicity

Methotrexate

■ Methotrexate

- Well documented effectiveness in steroid dependent Crohn's
 - Induction: MTX 25mg IM/week x16wks
 - 39% vs 19% (placebo) in clinical remission
 - Maintenance: MTX 15 mg IM/week
 - 65% vs 39% maintenance of steroid free remission at 40wks

MTX Risks

- Methotrexate
 - Nausea
 - Fatigue/malaise
 - Hepatotoxicity
 - Abnl LFT's ~25%
 - Fibrosis/cirrhosis rare
 - BM suppression
 - Hypersensitivity pneumonitis
 - 1% of patients
 - Teratogen
 - Increased risk of infection
 - Lymphoma risk is rare

MTX Risks

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Biologics

- Why are biologics called biologics?
 - These are medications that not made by simply mixing ingredients and creating chemical reactions to produce the medication
 - These therapies are made by using living organisms and even mammalian tissue and cells for reproduction

Biologics

■ Anti-Tnf

- Remicade (Infliximab) (made with mouse DNA)
- Humira (Adalimumab) (fully humanized ab)
- Cimzia (Certolizumab pegot) (monoclonal human ab)
- Simponi (Golimumab)

■ Anti-Integrins

- Tysabri (Natalizumab) (Used for MS and Crohn's)
- Entyvio (Vedolizumab)

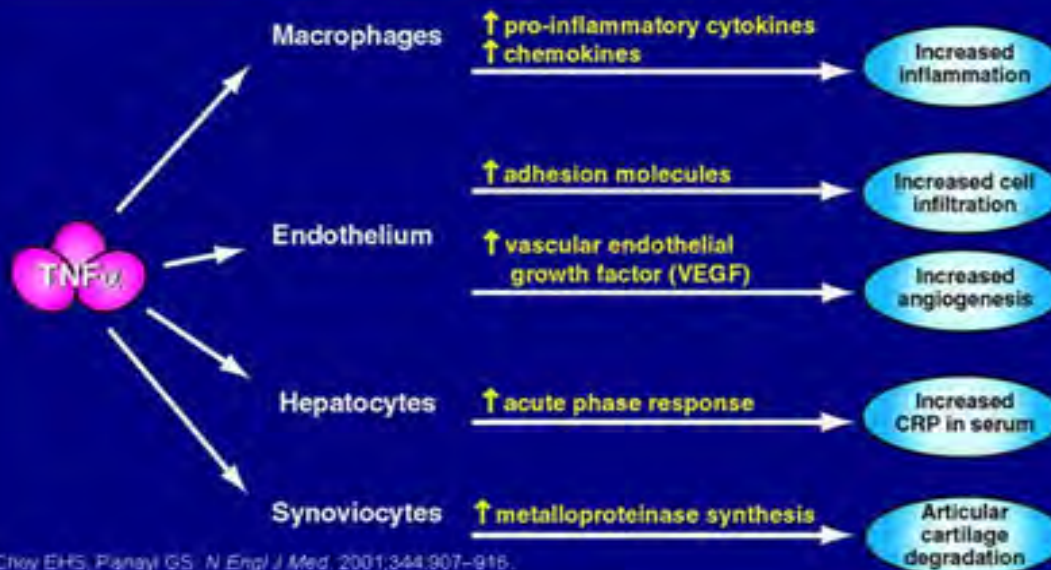
Biologics and Small Molecules

- Anti IL 12 & 23
 - Stelara (Ustekinumab)
- JAK Inhibitors (small molecule, not biologic)
 - Xeljanz (Tofecitinib)
- S1P Inhibitor (small molecule, not biologic)
 - Zeposia (Ozanimod)

TNF: Pro Inflammatory!!

Anti Tnf's: Block it!!!

Key Actions Attributed to TNF-alpha



Choy EH, Panayi GS. *N Engl J Med*. 2001;344:907-916.
Feldmann M et al. *Annu Rev Immunol*. 1996;14:397-440.
Gravallese EM, Goldring SR. *Arthritis Rheum*. 2000;43:2143-2151



Available Anti TNF Therapies

- Remicade: Infusion (Crohns and UC)
 - Infusion 5, 7.5, 10 mg/kg week 0, 2 and 6 wks then every 8wks thereafter.
 - Some patients require dose escalation
- Humira: Injectable (40 mg pen) (Crohns and UC)
 - 160 mg day 0, 80 mg week 2 then every 2 weeks thereafter
 - Some patients on weekly dosing
- Cimzia: Injectable (200 mg pen) Used in Crohn's
 - 400 mg day 0, 400 mg week 2 and week 4 then 400 mg monthly or 200 mg every 2 week
 - Medication dose not cross the placenta
- Simponi: Injectable (100 mg pen) Used in UC
 - 200 mg day 0, 100 mg week 2 and week 4, then 100 mg every 4 weeks
- ***Risk of developing antibodies with monotherapy: 15 – 20%
- ***Risk of antibodies with immunomodulator: 1%

Anti TNF agents: Safety Information

Risk of Serious Infections such as sepsis

Tuberculosis (TB), invasive fungal infections, and other opportunistic infections

Malignancies

Hypersensitivity

Hepatitis B Reactivation

Hepatitis

Neurologic Reactions

Hematologic Reactions

Congestive Heart Failure

Autoimmunity

Drug Interactions

Lupus like reaction

Psoriasis like reaction

Meta-analysis of lymphoma rate associated with anti-TNF agents

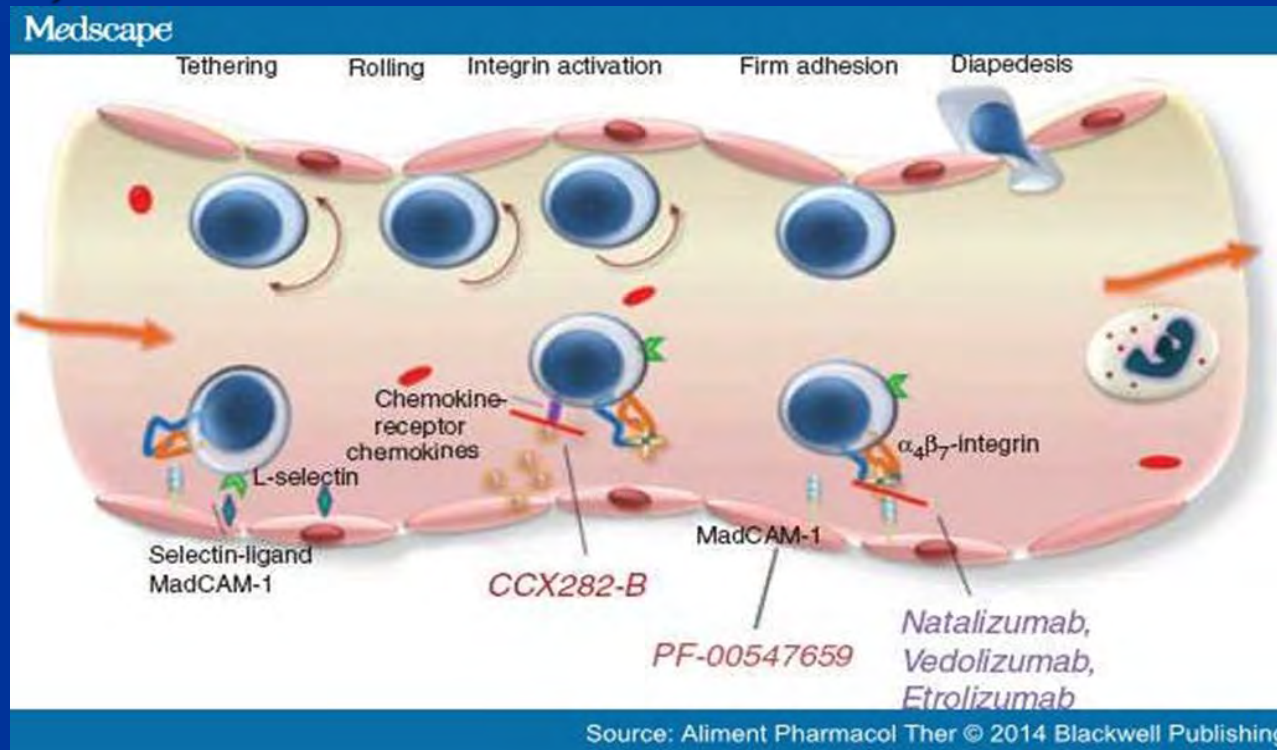
Event	Estimated Frequency (annual, pt-years)
Non-Hodgkin Lymphoma (baseline)	2/10,000
Non-Hodgkin Lymphoma (on IM)	6/10,000
Non-Hodgkin Lymphoma (on anti-TNF)	6/10,000
Hepatosplenic T-cell Lymphoma	Unknown
Death from sepsis	4/1000
Tuberculosis	5/10,000

Ries LAG, et al (eds). SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008.

Kandiel A, et al. Gut 2005;54(8):1121-1125 Siegel CA, et al. Gastroenterology 2008;134(4):A144. Abstract 970. Siegel CA, et al. Clinical Gastroenterology and Hepatology. 2006;4:1017-1024. Wolfe F, et al. Arthritis Rheum 2004;50(2):372-379.

Anti Integrin Therapy

- Integrins are molecules that act with adhesion molecules allowing white cells to leave the blood vessels, enter the soft tissue, and cause inflammation.



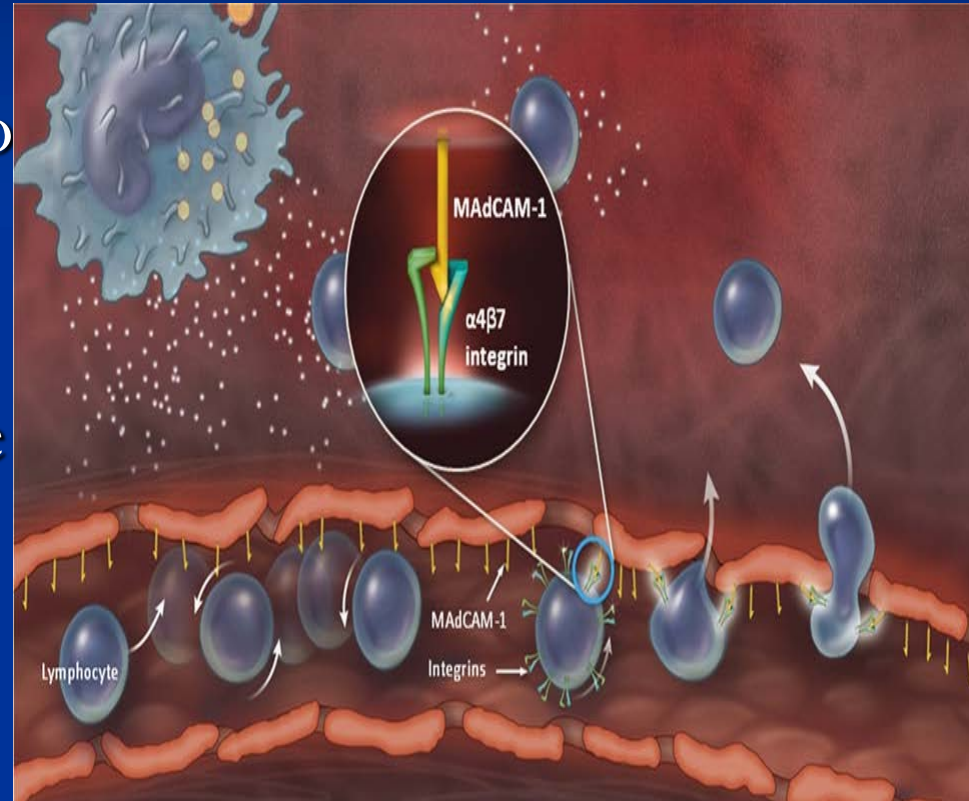
■ Tysabri (Natalizumab)

- Used in MS and not used as much in Crohns anymore
- It is a humanized monoclonal antibody against cell adhesion molecule α 4-integrin (crosses blood brain barrier).
- Risk of PML: Progressive Multifocal Leukoencephalopathy

■ Entyvio (Vedolizumab)

Vedolizumab

- Humanized IgG 1 monoclonal antibody to alpha4 beta7 integrin
- Modulates gut, but NOT brain lymphocyte trafficking
- Less risk of PML compared to natalizumab



Takeda website

Adverse Events With Vedolizumab

- Rare infusion-related reactions and hypersensitivity
 - 30-minute infusion and no postinfusion monitoring
- Not recommended in patients with active, severe infection until the infection is controlled
- No cases of PML have been observed
- Rare reports of elevations of transaminase and/or bilirubin
- Most common adverse reactions (incidence $\geq 3\%$ and $\geq 1\%$ higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities

IL 12 & 23 Blockers

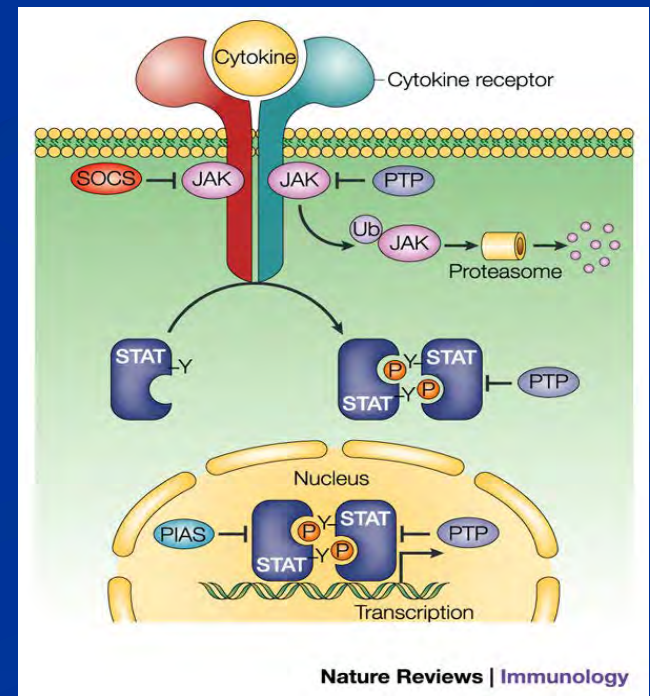
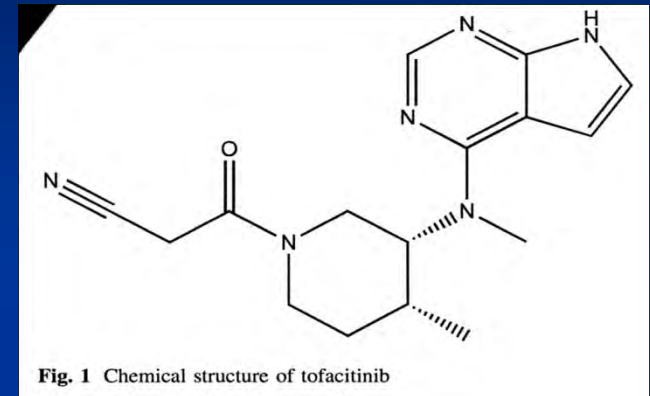
- Stelara (Ustekinumab)
 - Antibody to IL12 and IL23 (p40 subunit)
 - Approved for use in psoriasis
- Approved in 9/26/2016 for CD
- Approved in 10/21/2019 for UC

- Risks of Stelara:

- Increased risk of infections and reactivation of latent infections (bacterial, fungal and viral), and disseminated infections from mycobacteria, salmonella,
- Reactivation of latent TB
- Increased risk of malignancy
- Allergic reaction
- Reversible Posterior Leukoencephalopathy Syndrome a neurological disorder (patient instructed to notify us if they have headache, seizure, confusion and visual disturbances). Most common reactions include nasopharyngitis, URI, headache, fatigue, arthralgia and nausea.

Tofacitinib

- Small molecule
- JAK kinase inhibitor
 - Affinity for JAK 1 and JAK 3
 - Inhibits cytokine signaling
- Approved for RA that has not responded to MTX
- Metabolized by liver
 - (CYP3A4)
- Dosing: 10 mg BID orally initially
- Approved May 30, 2018



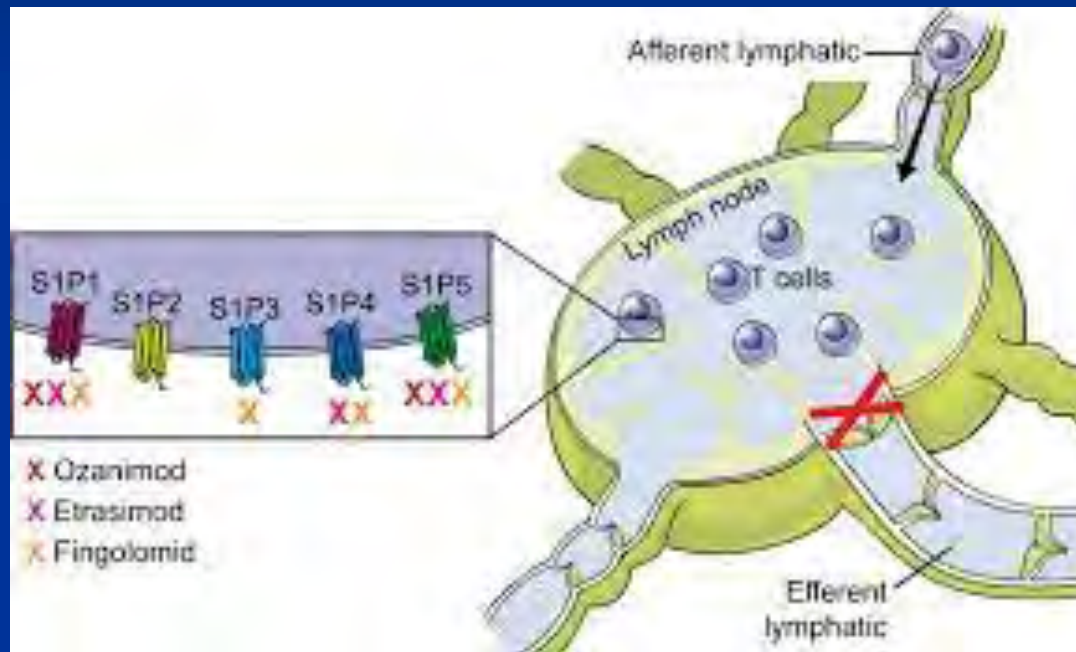
Tofacitinib adverse events

- Myelosuppression
- Lipid abnormalities
 - Increase in both LDL and HDL
 - Some patients need statins to control
- Serious infections
 - Pneumonia, cellulitis, zoster, UTI
- Liver function abnormalities
- Malignancies (including lymphoma)

Ozanimod

- Approved in May 2021 for UC
- Also works in Multiple Sclerosis
- It is an immunomodulator
- Inhibits Sphingomyelinase 1 Phosphate receptors and blocks the ability of lymphocytes to leave the lymph nodes
- S1P's are signaling lipids that are involved in inflammation, the permeability of blood vessels,

Mechanism of Action of Ozanimod



Side Effects of Ozanimod

- Can increase infection
- Can increase blood pressure
- Can cause changes in vision

IBD and Covid

- Based on international data of ibd patients with IBD, IBD patients are not at higher risks of developing bad infection with Covid
- IBD patients are not at higher risk even if they are on biologics
- IBD patients on prednisone did demonstrate worse disease if infected with covid
- IBD patients mount similar antibody response than general population

Points worth mentioning

- IBD is a complex and chronic disease
- You will encounter this at some point in your career no matter what you choose
- Always remember that in treating patients with chronic disease, establishing a trusting relationship with patients is key
- In medicine, don't forget why you chose this